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Performance of the Agency's scientific procedures: 2011 report for medicinal products for human use

Management Board meeting 22 March 2012

Executive summary

This is the yearly report to the Management Board on the Performance of the Agency's scientific procedures conveying descriptive statistics on initial marketing authorisation applications and extensions of indication for medicinal products with existing marketing authorisations that had a CHMP outcome in 2011.

The main findings are the following:

- In terms of eligibility for the centralised procedure for initial marketing authorisation applications, there has been a gradual drop in the number of biotech applications since 2009 and an increase of applications in indications mandatory for the centralised procedure. Moreover, the year 2011 saw the conclusion of the first Paediatric Use Marketing Authorisation (PUMA) application.
- There was a significant increase (52%; from 33 to 50 applications) in the number of stand-alone (i.e. non-generic/hybrid/biosimilar) initial marketing authorisation applications with an outcome in 2011 compared with 2010. The use of Scientific Advice among stand-alone applications increased to 76% (38/50) compared to the rather stable 55-60% reported during the previous three years. This analysis does not include the generic applications where scientific advice is generally lower than for applications with a more comprehensive development. The use of Scientific Advisory Group (SAG) or ad hoc expert group meetings was 20% (10/50 applications, vs 21% in 2010).
- New Active Substance applications (i.e. stand-alone applications for substances never previously authorised in the EU) have increased from 22 applications in 2010 to 30 in 2011. For these applications, the same failure rate (23%) was reported for 2011 and 2010 (compared with 40% in 2009). Stand-alone applications that do not include a New Active Substance (i.e. substances already previously authorised) increased comparatively even more (20 applications vs 11 in 2010).
- There was an increase (79%; from 24 to 43 applications) in the number of extension of indication applications with an outcome in 2011 compared with 2010 and their success rate was high (93%, vs 96% in 2010). Use of scientific advice for such applications (16% in 2011 vs 17% in 2010) was low in comparison with initial marketing authorisation applications. Consultation by the CHMP of SAG or ad hoc expert group meetings was also low (7% (3 applications) in 2011 vs 17% (4) in 2010) for extension of indication applications.

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Initial marketing authorisation applications

Methods

This annual report covers initial marketing authorisation applications with an outcome at CHMP during 2011 (from 01/01/2011 until 31/12/2011). This is defined as a positive or negative CHMP opinion or a withdrawal of a marketing authorisation/extension of indication application in 2011, irrespectively of the timing of the European Commission Decision, if any, on the application. Applications with a CHMP outcome in 2011 which already had a CHMP outcome in previous years (e.g. due to re-examination in 2011 of the initial CHMP Opinion reached at the end of 2010) are reported here despite having been reported already in past reports. The report does not cover applications for ancillary substances used in medical devices or Plasma Master File applications.

Two analyses have been conducted for initial marketing authorisation applications. The first focuses on eligibility to the centralised procedure. For the purposes of this analysis, multiple applications (i.e. applications which rely on the same dossier) have been counted only once. Similarly, the so called "informed consent" applications have been excluded. The data set for this analysis is referred to as the "Eligibility Set".

The second analysis focuses on outcome, procedural aspects and use of Scientific Advice. This analysis has been conducted based on two subsets. The first subset is referred to as "Stand-alone" set and excludes generic, hybrid and biosimilar applications. Stand-alone applications rely on their own data and do not make reference to the dossier of other medicinal products. As such, stand-alone applications do not contain multiple or informed consent applications either. The second subset further excludes applications for active pharmaceutical substances which had already been authorised in at least one EU/EEA country, independently of the indication for which they were authorised and whether authorised through centralised, mutual recognition, decentralised or purely national procedures. This subset is referred to as the "New Active Substance" (NAS) set in this report[1].

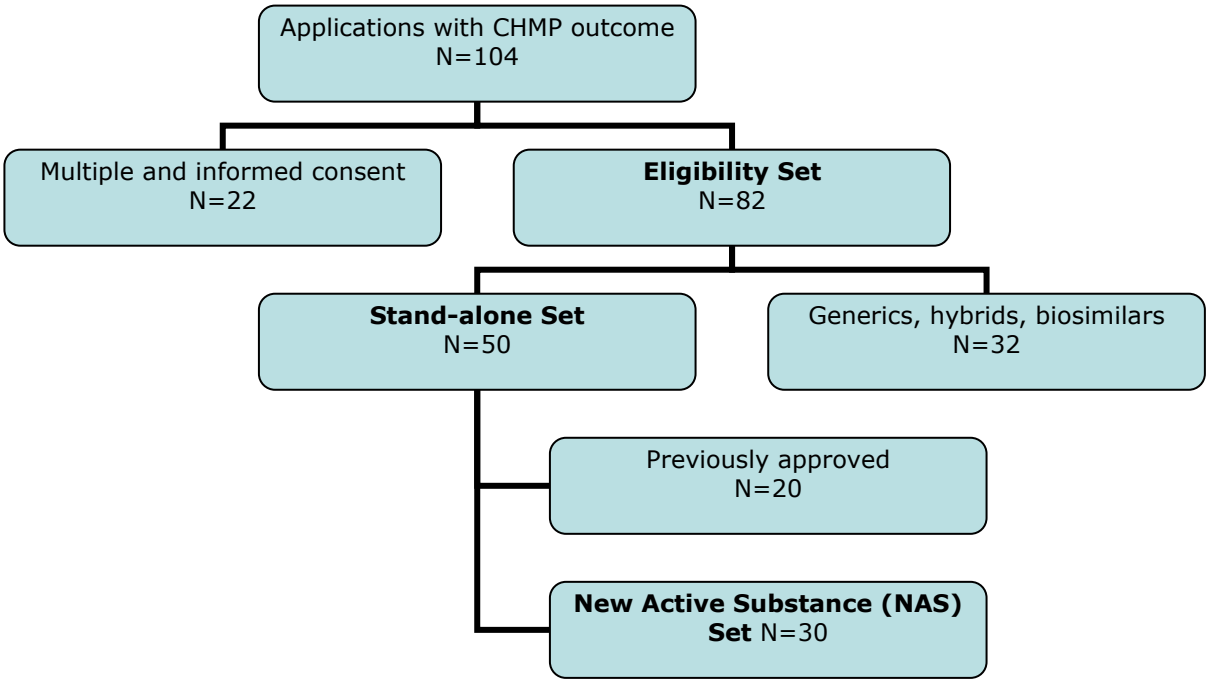
The Annex provides the benefit-risk balance as expressed by the CHMP in the final assessment of the NAS applications with an outcome in 2011. The narratives for applications with a CHMP Opinion (positive or negative) are copied from the published European Assessment Reports (EPARs). For withdrawn applications, the main concerns of the CHMP at the time of withdrawal, as captured in the relevant Q&A document for each product, are copied. Since not all EPARS are published as of to date (February 2011), the narratives for Caprelsa, Zelboraf and Glybera have not been included in this report.

[1] The term "new active substance" is defined in EU pharmaceutical legislation to include novel molecules that are either chemically-synthesised or from a biological source, as follows:
- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.
The definition of New Active Substance (NAS) used in this report further excludes biosimilar applications, as these were deemed not to be truly 'new' developments but rather similar to generic and hybrid applications. This modified definition of NAS is similar but not identical to the US FDA definitions of New Molecular Entity (NME) and New Biologic Entity (NBE). For more details, see Eichler H-G, *et al*. New drug approval success rate in Europe in 2009. Nat Rev Drug Discov. May;9(5):355-6 (2010).

Results

In 2011, there were a total of 104 initial marketing authorisation applications that reached an outcome in the Committee for Medicinal Products for Human Use (CHMP) scientific evaluation (see Figure 1). For three (3) of these (Orphacol, TOBI Podhaler and Movectro), a prior CHMP Opinion had been adopted in the previous year (2010). Excluding 22 multiple and informed consent applications, 82 applications were considered for the purposes of the analysis on the eligibility basis for the centralised procedure. Excluding 27 applications with a generic legal basis, 4 applications with a hybrid legal basis and one (1) application for a similar biological (biosimilar) medicine, 50 stand-alone applications were considered for the other two analyses, i.e. the analysis of all (50) stand-alone applications and the analysis of applications including a New Active Substance (NAS, 30/50 applications).

Figure 1: Schematic disposition of initial marketing authorisations concluded in 2011 and definition of analysis subsets (in bold)



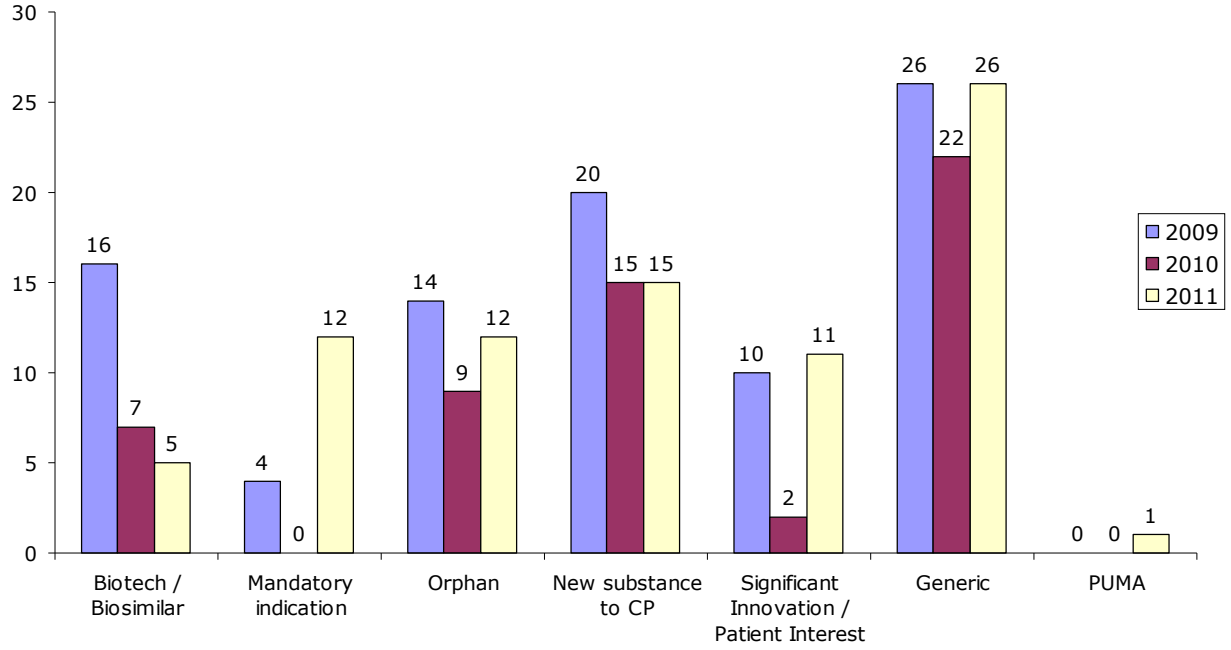
14 applications for orphan designated medicinal products reached an outcome at CHMP in 2011. Two (2) of these (Mercaptopurine Nova Laboratories and Plenadren) were hybrid applications and 12 were stand-alone applications. Half of these (6, 50%) included a NAS (Eurartesim, Glybera, Kalbitor, Luveniq, Tekinex, Vyndaqel) and the other half (6, 50%) included previously authorised substances (Bronchitol, Cinryze, Colobreathe, Orphacol, TOBI Podhaler, Votubia).

14 applications submitted by Small and Medium Enterprises (SMEs) had a CHMP outcome in 2011. Two (2) of these were generic applications (Sepioglin, Topotecan Eagle) and 4 were hybrid applications (Buccolam, Mercaptopurine Nova Laboratories, Methylthioninium chloride Proveblue, Plenadren). There were 8 stand-alone applications, 4 of which included previously authorised active substances (Ameluz, Bronchitol, Orphacol, Pravafenix) and 4 included a NAS (Beprana, Glybera, Luveniq, Tekinex).

Eligibility Set (N=82)

Eligibility criteria for 82 applications with an outcome in 2011 are described in Figure 2 alongside the data reported in 2010 and 2009 (multiple and informed consent applications excluded).

Figure 2: Eligibility criteria for initial marketing authorisation applications (eligibility set)



The products considered eligible for the centralised procedure are listed by category below:

- Biotech (5): Nulojix, Yervoy, XGEVA, Ozespa, Epostim (biosimilar)

- Mandatory indication (12): Gilenya, Jevtana, Halaven, Trajenta, Edurant, Eviplera, Caprelsa, Zytiga, Incivo, Zelboraf, Komboglyze, Janacti

- Orphan (12): Luveniq, Glybera, Tekinex, Plenadren, Mercaptopurine Nova Laboratories, Kalbitor, Vyndaqel, Bronchitol, Eurartesim, Colobreathe, Orphacol, TOBI Podhaler

- New substance to CP[2] (15): Eliquis, Beprana, Fampyra, Trobalt, Pravafenix, Rasitrio, Benlysta, Dificlir, Edarbi, Vepacel, Esmya, Victrelis, Rasilamlo, Yellox, Vibativ

- Significant Innovation / Patient Interest (11): Hizentra, Bydureon, Sumatriptan Galpharm, Votubia, Ameluz, Movectro, Dexdor, Methylthioninium chloride Proveblue, Zoely, Cinryze, Joicela

- Generic (26): Doxorubicin SUN, Rivastigmine Actavis, Temozolomide SUN, Pioglitazone Teva, Pioglitazone ratiopharm, Sepioglin, Paglitaz, Pioglitazone Accord, Pramipexole Accord, Pioglitazone Actavis, Levetiracetam Teva, Levetiracetam Actavis, Levetiracetam Accord, Levetiracetam ratiopharm, Repaglinide Accord, Efavirenz Teva, Desloratadine Teva, Desloratadine Actavis, Topotecan SUN, Desloratadine ratiopharm, Dasselta, Matever, Levetiracetam Actavis Group, Levetiracetam SUN, Topotecan Eagle, Docetaxel Mylan

- PUMA (1): Buccolam

It should be noted that the generic subset (26 applications) above includes applications granted eligibility to the centralised procedure as pertaining to generics of centrally authorised products. Stand-alone applications further exclude 1 generic (Sumatriptan Galpharm) and 4 hybrid applications (Buccolam, Methylthioninium chloride Proveblue, Mercaptopurine Nova Laboratories, Plenadren) of previously non-centrally authorised medicinal products. The biosimilar Epostim is excluded, as well.

[2] This eligibility basis is generally referred to as New Active Substance meaning that the substance is new to the centralised procedure although it may have been previously authorised via national procedures in the EU/EEA. In order to avoid confusion, this eligibility basis has been renamed 'New substance to CP' for the purposes of this report.

Outcome of Marketing Authorisation Applications and Scientific Advice

Stand-alone Set (N=50)

Of the 50 stand-alone applications (compared to 33 applications in 2010), 40 (80%) reached a positive CHMP outcome leaving 10 (20%) unsuccessful (negative opinion or withdrawn). 4 (Glybera, Kalbitor, Luveniq and Tekinex) of the 12 orphan medicinal products had an unfavourable outcome as did 4 (Beprana, Glybera, Luveniq and Tekinex) of the 8 applications that were submitted by small and medium sized companies (SMEs). Glybera was the only "advanced therapy" application in 2011.

3 applications were approved conditionally (Caprelsa, Fampyra and Votubia). Vyndaqel was approved under exceptional circumstances and Orphacol received a revised positive CHMP Opinion recommending an approval under exceptional circumstances (EC Decision pending). Incivo, Victrelis and Zytiga were subject to accelerated assessment.

12 oral explanations (plus 4 more for generics/hybrids) took place where the applicant had the opportunity to clarify certain issues in front of the CHMP (for Beprana, Bronchitol, Eurartesim, Fampyra, Glybera, Joicela, Kalbitor, Luveniq, Movectro, Pravafenix, Rasilamlo, Vibativ; generics Doxorubicin SUN, Topotecan Eagle, Sumatriptan Galpharm and hybrid Plenadren).

During the assessment of 10 (20%) applications (Benlysta, Caprelsa, Eurartesim, Fampyra, Gilenya, Glybera, Luveniq, Movectro, XGEVA, Yervoy) the CHMP convened scientific advisory group (SAG) meetings or ad hoc expert group meetings prior to final recommendation (a SAG meeting was also convened for the Plenadren hybrid application).

Scientific Advice was given for 38/50 applications (76%, compared with 55-60% in the previous three years), 30 (79%) of which had a positive CHMP outcome. Of the 8 (21%) of applications with an unfavourable outcome despite having received Scientific Advice, half (4, 50%) pertained to designated orphan medicines (Glybera, Kalbitor, Luveniq, Tekinex) and half (4, 50%) were submitted by SMEs (Beprana, Glybera, Luveniq, Tekinex).

Table 1: Outcomes of initial marketing authorisation applications (Stand-alone Set, N=50)

	Positive[3]	Negative/Withdrawn[3]	Total[4]
Stand-alone Set	40 (80%)	10 (20%)	50 (100%)
Orphan product	8 (67%)	4 (33%)	12 (24%)
Non-Orphan product	33 (87%)	5 (13%)	38 (76%)
SME applicant	4 (50%)	4 (50%)	8 (19%)
Non-SME applicant	36 (86%)	6 (14%)	42 (81%)
Conditional MA	3	n/a	3 (6%)
MA Except Circum	2	n/a	2 (4%)
Normal MA	35	10	45 (90%)
SA given	30 (79%)	8 (21%)	38 (76%)
SA not given	10 (83%)	2 (17%)	12 (24%)

[3] Numbers in parentheses denote percentages of total applications in the row category
[4] Numbers in parentheses denote percentages of total applications

New Active Substance Set (N=30)

30 (60%) out of 50 stand-alone applications in 2011 (compared with 22 applications in 2010) were considered as containing a NAS (Table 2). 20 stand-alone applications did not contain a NAS (compared with 11 in 2010). The success rate of applications containing a NAS was 77% in 2011, the same as in 2010 (compared with 60% in 2009).

Table 2: Outcomes of initial marketing authorisation applications (NAS Set, N=30)

	Positive[5]	Negative/Withdrawn[5]	Total[6]
NAS Set	23 (77%)	7 (23%)	30 (100%)
SME applicant	0 (0%)	4 (100%)	4 (13%)
Non-SME applicant	23 (88%)	3 (12%)	26 (87%)
SA given	19 (73%)	7 (17%)	26 (87%)
SA not given	4 (100%)	0 (0%)	4 (13%)

In the national decentralised procedure one (1) new active substance reached an outcome in 2011 compared with 4 in 2010.

Applications for extension of indication

Methods

The analysis conducted pertained to applications for extension of indication for centrally authorised products (CAPs) that reached an outcome (positive or negative Opinion or withdrawal of application) at CHMP in 2011 (01/01/2011-31/12/2011). Multiple and informed consent applications were not considered, similarly to initial marketing authorisation applications above. Applications for extension of indication for generics, hybrids and biosimilars in follow up to respective changes in the indication of reference products were not considered, either.

With regard to outcome, a differentiation is made between applications that both received positive CHMP Opinion and SmPC changes pertained to section 4.1 (Therapeutic indications) and applications with a formally positive CHMP Opinion but with SmPC changes excluding a change in the therapeutic indication (most commonly with changes in section 5.1 of the SmPC).

The Annex provides the benefit-risk balance as expressed by the CHMP in the final assessment of the extensions of indication for which the Committee gave positive opinions and changes were introduced in the Therapeutic indications section (4.1) of the SmPC. The narratives are copied from the published EPARs. Since not all EPARS are published as of to date (February 2012), the narratives for Erbitux, Herceptin (neoadjuvant breast cancer), Nevanac, Galvus, Rebif and Procoralan have not been included in this report. Moreover, the report does not contain the narratives for Macugen (withdrawn), Cymbalta and Xyrem (negative CHMP Opinion) as well as Advate, Levemir, Victoza and Viread (positive CHMP Opinion but no changes to the therapeutic indication).

[5] Numbers in parentheses denote percentages of total applications in the row category
[6] Numbers in parentheses denote percentages of total applications

Results

In 2011, the CHMP completed the assessment of 50 applications for extensions of indications for centrally authorised products (CAPs). Six (6) of these were duplicate applications and there was one extension of indication for a biosimilar (Retacrit). The remaining 43 applications were thus taken into account in the subsequent analyses (analysis set, see Figure 2). 40 out of the 43 applications (93%) reached a positive opinion (compared with 96% in 2010). For four (4) procedures the positive opinion related to updates of the product information other than section 4.1 of the SmPC (Therapeutic indications). One procedure was withdrawn before CHMP opinion and for two procedures a negative opinion was adopted.

Scientific Advice was given in relation to the sought new indication for 7 of the 43 procedures (16%, compared with 17% in 2010) and scientific advisory group (SAG) or ad hoc expert group meetings were convened during the review of 3 extension of indication applications (7%). Results are summarised in Table 3.

Figure 2: Schematic disposition of extension of indication applications concluded in 2011

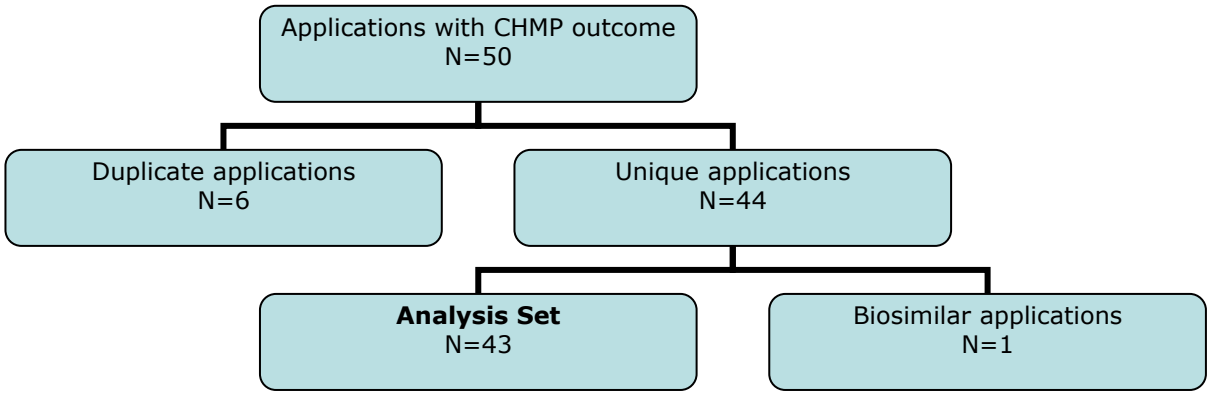


Table 3: Outcomes of extension of indication applications (Analysis Set, N=43)

	Positive with indication change[7]	Positive without indication change[7]	Negative/Withdrawn[7]	Total[8]
All applications	36 (84%)	4 (9%)	3 (7%)	43 (100%)
SA given	6 (86%)	0 (0%)	1 (14%)	7 (16%)
SA not given	30 (83%)	4 (11%)	2 (6%)	36 (84%)

[7] Numbers in parentheses denote percentages of total applications in the row category
[8] Numbers in parentheses denote percentages of total applications

ANNEX

Table 4: Initial marketing authorisation applications for products not considered to contain a NAS with CHMP outcome in 2011 (N=20)

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
Ameluz	5-aminolevulinic acid hydrochloride	Significant innovation/patient Interest	Actinic keratosis	Positive by consensus
Bronchitol	mannitol	Orphan medicinal product	Cystic fibrosis	Positive after appeal by majority
Bydureon	exenatide	Significant innovation/patient Interest	Type II diabetes	Positive by consensus
Cinryze	c1 inhibitor	Significant innovation/patient Interest	Angioedema due to C1 inhibitor deficiency	Positive by consensus
Colobreathe	colistimethate sodium	Orphan medicinal product	cystic fibrosis	Positive by consensus
Dexdor	dexmedetomidine	Significant innovation/patient Interest	Sedation	Positive by consensus
Esmya	ulipristal	New substance to CP**	Uterine fibroids	Positive by consensus
Hizentra	human normal immunoglobulin	Significant innovation/patient Interest	primary immunodeficiency syndromes, severe secondary hypogamma-globulinaemia	Positive by consensus
Janacti	sitagliptin / pioglitazone	Mandatory Therapeutic Indication	Type II diabetes	Withdrawn prior to Opinion
Komboglyze	saxagliptin / metformin	Mandatory Therapeutic Indication	Type II diabetes	Positive by consensus
Movectro	Cladribine	Significant innovation/patient interest	Multiple Sclerosis	Negative after appeal by majority. Initial negative Opinion in September 2010
Orphacol	Cholic acid	Orphan medicinal product	Inborn errors in primary bile acid synthesis	Positive by consensus. Revised Opinion in April 2011. Initial positive Opinion in December 2010
Pravafenix	fenofibrate / pravastatin	New substance to CP**	Coronary Heart Disease, dyslipidaemia	Positive by consensus
Rasilamlo	aliskiren / amlodipine	New substance to CP**	Essential hypertension	Positive by consensus
Rasitrio	aliskiren / amlodipine / hydrochloro-thiazide	New substance to CP**	Essential hypertension	Positive by consensus
TOBI Podhaler	Tobramycin	Orphan medicinal product	Cystic fibrosis	Positive by consensus. Revised Opinion in April

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
				2011. Initial positive Opinion in September 2010
Vepacel	influenza virus (H5N1-whole virion, non-adjuvanted, Vero cell-derived, inactivated, containing antigen of A/Vietnam/1203/ 2004)	New substance to CP**	influenza vaccine	Positive by consensus
Votubia	everolimus	Significant innovation/patient interest	Tuberous sclerosis	Positive by consensus
XGEVA	Denosumab	Biotech medicinal product	Bone metabolism	Positive by consensus
ZOELY	nomegestrol acetate/estradiol	Significant innovation/patient interest	Oral contraception	Positive by consensus

* INN: International non-proprietary name
** CP: centralised procedure – this eligibility basis is referred to as 'New Active Substance', but it has been renamed for the purposes of this report to avoid confusion

Table 5: Initial marketing authorisation applications for products considered to contain a NAS with CHMP outcome in 2011 (N=30)

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
A. Positive Outcomes (n=23)				
Benlysta	belimumab	New substance to CP*	Systemic lupus erythematosus (SLE)	Positive by consensus
Caprelsa	vandetanib	Mandatory Therapeutic Indication	Medullary thyroid cancer	Positive by consensus
Dificlir	fidaxomicin	New substance to CP*	Clostridium difficile infections	Positive by consensus
Edarbi	azilsartan medoxomil	New substance to CP*	Essential hypertension	Positive by consensus
Edurant	rilpivirine	Mandatory Therapeutic Indication	HIV infection	Positive by consensus
Eliquis	apixaban	New substance to CP*	Venous thrombo-embolic events (VTE)	Positive by consensus
Eurartesim	dihydroartemisinin / piperaquine phosphate	Orphan medicinal product	Malaria	Positive by majority
Eviplera	emtricitabine / rilpivirine / tenofovir disoproxil	Mandatory Therapeutic Indication	HIV infection	Positive by consensus
Fampyra	fampridine	New substance to	Multiple Sclerosis	Positive after appeal

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
		CP*		by majority
Gilenya	fingolimod hydrochloride	Mandatory Therapeutic Indication	Multiple sclerosis	Positive by consensus
Halaven	eribulin mesylate	Mandatory Therapeutic Indication	Breast cancer	Positive by consensus
INCIVO	telaprevir	Mandatory Therapeutic Indication	Chronic hepatitis C (genotype 1)	Positive by consensus
Jevtana	cabazitaxel	Mandatory Therapeutic Indication	Prostate cancer	Positive by consensus
Nulojix	belatacept	Biotech medicinal product	prophylaxis of renal graft failure and dysfunction	Positive by consensus
Trajenta	linagliptin	Mandatory Therapeutic Indication	Type 2 diabetes	Positive by consensus
Trobalt	retigabine	New substance to CP*	Epilepsy	Positive by consensus
Vibativ	telavancin	New substance to CP*	pneumonia	Positive by majority
Victrelis	boceprevir	New substance to CP*	hepatitis C	Positive by consensus
Vyndaqel	tafamidis	Orphan medicinal product	transthyretin amyloidosis	Positive by consensus
Yellox	bromfenac	New substance to CP*	ocular inflammation	Positive by consensus
Yervoy	ipilimumab	Biotech medicinal product	melanoma	Positive by consensus
Zelboraf	vemurafenib	Mandatory Therapeutic Indication	melanoma	Positive by consensus
Zytiga	abiraterone	Mandatory Therapeutic Indication	prostate cancer	Positive by consensus
A. Negative Outcomes (n=7)				
Beprana	naproxcinod	New substance to CP*	Arthritis, osteoarthritis	Withdrawn prior to Opinion
Glybera	alipogene tiparvovec	Orphan medicinal product	Hyperlipidaemia	Negative after appeal by majority
Joicela	lumiracoxib	Significant innovation/patient interest	Arthritis, osteoarthritis	Withdrawn prior to Opinion
Kalbitor	ecallantide	Orphan medicinal product	Hereditary angioedema (HAE)	Withdrawn prior to Opinion
Luveniq	voclosporin	Orphan medicinal product	Non-infectious uveitis	Withdrawn after appeal
Ozespa	briakinumab	Biotech medicinal product	Psoriasis	Withdrawn prior to Opinion
Tekinex	omacetaxine mepesuccinate	Orphan medicinal product	Chronic myeloid leukaemia	Withdrawn prior to Opinion

* CP: centralised procedure – this eligibility basis is referred to as 'New Active Substance', but it has been renamed for the purposes of this report to avoid confusion

1. Benefit Risk assessments - from the EPAR of the New active substance (NAS) applications with positive CHMP outcomes in 2011 (as available on 01 February 2012)

1.1. Benlysta

Benefits

- Beneficial effects

There are currently no established regulatory tools to evaluate the efficacy of drugs for the treatment of patients with SLE. However, based on the complexity of the disease, it is agreed that a single tool might not be sufficient in the assessment of disease activity in individual patients.

Both belimumab Phase 3 trials (C1056 and C1057) achieved a significantly higher responder rate for the treatment dose applied for (10 mg/kg) compared with placebo. Belimumab treatment demonstrated beneficial effects with higher rates of reductions in disease activity in a population with involvement of vascular, musculoskeletal, immunology, and mucocutaneous organs. In study C1056, belimumab 10 mg/kg, in addition to standard therapy, yielded 9.41% (p=0.0207, OR=1.52, 95% CI= 1.07, 2.15) more responders at Week 52 as compared to standard therapy only. In study C1057, 14% (p=0.0006, OR=1.83, 95% CI= 1.30, 2.59) more responders were seen.

Analyses of SLE flare were performed according to the modified SLE Flare Index. In study C1056, no clinically relevant benefit with regard to time to first flare or frequency of flares could be shown for the recommended belimumab treatment dose. In study C1057 some benefits with regard to time to first flare and frequency of flares could be shown for the 10 mg/kg group.

Efficacy results from placebo-controlled treatment with belimumab through 18 months (76 weeks) showed a diminished response rate from 9.41% to 6.10% and the difference was no longer statistically significant.

While uncertainty remains about the robustness of the results for the primary endpoint in the overall patient population, the results of the additional analyses showed a clinically relevant treatment effect in patients with high disease activity (anti-dsDNA antibodies and low levels of C3 and/or C4). In the subset of patients with low complement (plus antiDNA-), belimumab showed similar efficacy to that seen in the overall population, but the numbers are limited to draw any conclusion. The data further reinforce the restriction of the indication to those patients with high disease activity (e.g antiDNA+/low complement levels). A more robust benefit is seen in this subset of patients whilst limited, or even null, benefit might be expected in the population with anti-dsDNA negative and/or normal complement levels.

- Uncertainty in the knowledge about the beneficial effects.

The feasibility of describing the appropriate target population in an indication wording was discussed during an ad hoc expert meeting. In principle, the experts concurred with an indication wording that restricts the use to patients with high disease activity. Ideally disease activity should be assessed using a validated disease index rather than laboratory values. However, the proposal from the company to use laboratory tests (anti-dsDNA, low C3/C4) only to define disease activity, rather than questionnaire, was considered acceptable for the indication wording.

The effect of belimumab has only been demonstrated in a patient population with mainly musculoskeletal, vascular, mucocutaneous and haematological involvement. Whether the effect will remain in patients with involvement of vital organ/systems (cardiovascular/respiratory, CNS and renal)

is unknown. The reason for not including patients with active nephritis or CNS involvement in the Phase 3 trials seems justified but does not change the fact that data in this aspect is insufficient for conclusions on belimumab effect on key target organs. A Phase 2 trial specific to lupus nephritis is planned, but does not cover for the current lack of data in more vital organ domains. Therefore, the CHMP concluded that the effect of belimumab has only been demonstrated in a patient population with mainly musculoskeletal, vascular, mucocutaneous and haematological involvement. Whether the observed modest effect would remain in patients with other key organ involvement (mainly renal and CNS) is unknown. This is clearly reflected in the labelling and a post-approval study will evaluate the efficacy and safety of belimumab in patients with severe active lupus nephritis.

There are some uncertainties concerning optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon. The absence of information has been added as important missing information in the RMP and Applicant has committed to study treatment holidays and rebound phenomenon in upcoming studies.

The chronic use of CS was high in both studies: 76% of patients in Study C1056 and 96% in Study C1057, with half of the subjects being on high CS doses, i.e. >7.5 mg/d. The CHMP questioned whether this could be considered as standard-of-care in all parts of the EU. A corresponding question was therefore asked to the ad hoc expert group. In their response, the experts acknowledged the variability of corticosteroid use across Europe. The experts were not concerned with high use of CS in the belimumab clinical trials and did not consider the pattern of CS use to impact on the ability to extrapolate the study results to the intended EU target population.

Response rates varied according to race. The observed difference in effects between races was also discussed during the ad hoc expert meeting. The issue of a possible difference in effect between races was not of concern to the experts as this was considered manageable in clinical practice. However, the experts welcomed the company's commitment to conduct a post-approval study to address this question.

Only 1.6% of the studies population were elderly patients. Considering that in up to 15% of cases, SLE appears in patients over 55 years and that the disease course and response to treatment differs from that seen in adults, no firm conclusions regarding efficacy in elderly can be made. This is clearly reflected in the labelling.

Risks

- Unfavourable effects

In the placebo-controlled IV SLE CRD studies (i.e. primary safety population), the incidence and distribution of AEs was generally fairly similar between the placebo group and the 1 mg/kg and 10 mg/kg belimumab groups. Common events that were reported slightly more frequently in both belimumab groups compared with placebo included: nausea, diarrhoea, nasopharyngitis, bronchitis, pain in extremity, and depression. Other events that were more commonly reported in the 10 mg/kg belimumab group compared with placebo included leukopenia, pyrexia, cystitis, viral gastroenteritis, migraine, and insomnia. However, the differences in incidence between the treatment groups for these common events were small. Similarly, the incidence of SAEs in the controlled SLE studies was similarly distributed across the treatment groups.

In the long-term open-label continuation studies, the overall incidence of events did not appear to increase over time, and some events declined. Relatively few subjects discontinued because of an AE.

The adverse event data in the RA studies (secondary safety population) were consistent with the IV SLE CRD studies.

A safety concern is the occurrence of possible hypersensitivity reactions or other infusion related reactions. In the IV SLE CRD studies, 2.1% of subjects in the 10 mg/kg belimumab group had an AE that was coded as 'infusion-related reaction' compared with 1.3% in the 1 mg/kg group and 0.7% of subjects treated with placebo. Also, 0.4% of subjects in the 10 mg/kg group and 0.3% of subjects in the 1 mg/kg group had a severe infusion related reaction compared with 0.1% of subjects who received placebo.

Four subjects (0.6%) in the 10 mg/kg belimumab group in these studies experienced SAEs of infusion related reaction combined with 2 subjects (0.3%) in the 1 mg/kg group and 2 (0.3%) in the placebo group. In addition, 2 (0.3%) subjects in the 10 mg/kg and 2 (0.3%) subjects in the 1 mg/kg group had SAEs coded as anaphylactic reaction or drug hypersensitivity reaction, compared with none in the placebo group. Two of the subjects with an anaphylactic reaction also developed angioedema. All events were considered at least possibly related to study drug.

The risk of adverse infusion reactions was increased with belimumab compared with placebo. Some of the events were life-threatening in nature and required immediate and appropriate emergency room management. Overall, the incidence of serious reactions was approximately 1%, both for the 1 mg/kg and the 10 mg/kg dose. The mechanism of these reactions needs to be further elucidated and the Applicant has committed to evaluate data on infusion reactions reported from ongoing clinical trials as well as to perform a retrospective analysis of the two pivotal studies as part of the agreed RMP. A warning regarding infusion reactions and hypersensitivity is included in the SPC.

Since belimumab is a biologic agent that inhibits the survival and differentiation of B cells, additional important events were considered the risk of infection and malignancy. These events were further analyzed by the Applicant as AEs of special interest.

In the IV SLE CRD studies, the incidence of infections was generally comparable between the 1 mg/kg and 10 mg/kg belimumab treatment groups compared with placebo, with the exception of bronchitis and nasopharyngitis, which were slightly more common in the belimumab groups. The incidence of serious bronchitis was also higher for belimumab (0.4% in the 10 mg/kg group compared with 0.1% for placebo).

The incidence of sepsis was low but also somewhat higher for belimumab compared with placebo (0.7% for the 10 mg/kg group compared with 0.4% for placebo). There were five SAEs of sepsis (0.7% of subjects) in the belimumab 10 mg/kg group compared with one subject (0.1%) in the placebo group.

Overall, there were no significant differences regarding Grade 3 or Grade 4 lymphopenia, neutropenia and IgG levels between the placebo and the belimumab 1 mg/kg or 10 mg/kg groups in the controlled SLE studies. However, subjects in the belimumab groups who experienced Grade 3 or Grade 4 lymphopenia, neutropenia, or low IgM or IgG exhibited slightly higher rates of infections versus placebo and versus subjects without these abnormalities.

- Uncertainty in the knowledge about the unfavourable effects

Belimumab is a human monoclonal antibody that specifically binds and inhibits the activity of soluble human BLyS, a member of the TNF ligand superfamily. BLyS promotes B-cell differentiation, proliferation, and Ig class switching and survival. Risks that may be associated with the use of immunomodulators in general are the risk of (opportunistic) infections and the potential risk for malignancy. It is not known to what degree these potential concerns may also apply to belimumab.

In general, in the placebo-controlled IV SLE CRD studies, the incidence and distribution of AEs was generally fairly similar between the placebo group and the 1 mg/kg and 10 mg/kg belimumab groups, which would be indicative of a generally favourable safety profile. However, it is possible that the

concomitant treatment with other immunosuppressants, such as corticosteroids, could have diminished the detection of certain safety signals.

A major increase in infection incidence was not observed in the belimumab studies. The number of deaths with relation to sepsis in the controlled studies was slightly higher in the belimumab groups, compared with placebo. However, a possible relationship to belimumab was not always clear. Indeed, belimumab was used as an add-on treatment to standard of care SLE therapy, which typically includes other immunosuppressant drugs. Similarly, there were a few SAEs of opportunistic infection (including two cases of CMV infection) where a possible contributory role by belimumab could not be excluded. However, these subjects received other immunosuppressive therapies as well.

A longer follow up is needed to clarify the additional risk of infection with prolonged belimumab treatment. Also, the extent of B-cell suppression with continued treatment remains to be clarified. A submitted update for the ongoing Study C1056, which included efficacy data for Week 76, showed a continued decline in B-cell subsets compared with Week 52. It is not known whether this decline eventually stabilizes with ongoing treatment.

While cases of progressive multifocal leukoencephalopathy (PML) have been reported for other immunosuppressive drugs, to date no cases have been reported for belimumab.

In addition, the efficacy and safety of vaccinations in patients treated with belimumab has not been clarified. The Applicant has committed to perform a post-approval study to assess the efficacy of concurrent vaccination in patients receiving belimumab treatment.

There were slightly more reports of psychiatric disorders in the belimumab groups compared with placebo. The differences were small but the reasons are unclear, considering that belimumab primarily acts on B cells. Long-term follow-up data will be of value to determine whether there is a signal.

No particular trends regarding malignancy were observed in the relatively short observation period of 52 weeks of controlled data. In general, it is known that the risk of malignancy is greater in patients with SLE compared with a non-SLE population. Across the Phase 2 and 3 IV SLE studies (LBSL02, C1056, C1057, and the open-label study LBSL99), the rate of malignant neoplasms (excluding NMSC) per 100-subject years with belimumab was similar to the rate observed in a large international SLE cohort study. Overall, no conclusions can be drawn with some certainty until more and longer duration follow-up data are available.

No particular trends regarding malignancy were observed in the relatively short observation period of 52 weeks of controlled data. However, malignancies are included as a potential risk in the RMP and the incidence of malignancies will be evaluated in a post-approval safety study evaluating the long-term safety of IV belimumab in SLE patients.

Benefit-risk balance

- Importance of favourable and unfavourable effects

There is an unmet medical need for novel options in SLE treatment. No new drugs have been approved for the indication SLE in many years. While a number of treatment options are available for SLE, many patients have incompletely controlled disease, resulting in irreversible damage to internal organ system. Standard therapy includes corticosteroids, anti-malarial agents, non-steroidal anti-inflammatory drugs, cytotoxic agents and immunosuppressive or immunomodulatory agents used in cancer or transplantation, which all causes unfavorable side-effects. Consequently, a new drug providing additional disease control or presenting a more favorable safety profile would be considered of clinical value.

Alternative analyses performed for the two pivotal Phase 3 studies support a clinically relevant treatment effect of belimumab in addition to standard therapy in patients with high disease activity. A substantially increased likelihood of a treatment response has been shown for the subpopulation of patients with anti-dsDNA antibodies and low complement levels.

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The mechanism of these reactions has not been clarified but the Applicant has committed to conduct a study as part of the RMP to further elucidate this finding. In any case, this is not considered a major obstacle against the use of belimumab if appropriate preventive measures are taken as stated in the SmPC.

Potential concerns relating to the long-term use of immunomodulators in general are the risk for (opportunistic) infections and the potential risk for malignancy. It is not known to what degree these potential concerns also apply to a compound such as belimumab. Given that SLE is a life-long illness that requires chronic treatment, identification of such risks is of great importance. The Applicant has committed to collect long-term safety data through post-approval committments.

- Benefit-risk balance

Despite improved treatment options for patients with SLE, there is still an unmet medical need in this indication for which no new medicinal products have been approved in several decades. Belimumab has shown to be effective as an add-on therapy in a subgroup of SLE patients that have a high degree of disease activity (e.g positive anti dsDNA and low complement) despite standard therapy.

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The long-term safety of IV belimumab treatment in SLE patients will be evaluated in a large post-approval safety study. In addition, other known and potential risks as well as important missing information are adequately reflected in the SPC and appropriate pharmacovigilance measures are included in the RMP.

The combined favourable effects of belimumab treatment are considered to outweigh the unfavourable effects.

Discussion on the benefit-risk balance

Results from alternative analyses support a larger effect in patients with high disease activity indicating that belimumab could be of value for some patients. Based on available data it is acknowledged that a larger and clinically relevant benefit is shown for the subpopulation of patients with high disease activity (e.g.anti-dsDNA and low complement levels). The safety profile for this subgroup of patient does not appear to be significantly different to the safety profile for the overall study population and consequently the benefit-risk is considered positive.

Overall, the study results indicate that 52 weeks belimumab treatment may provide an additional treatment benefit of value for some patients. However, considering the initial pre-specified analyses and the alternative post hoc analyses provided, the effect demonstrated for the overall study population must be considered modest: in the primary responder analyses there was only about a 10 percentage difference between treatments; the support from the analyses of the secondary endpoints is weak.

In the high activity subgroups, however, the magnitude of effect was more pronounced and supported by consistent significant results for secondary endpoints. The data on maintenance of effect was also

more convincing in these subgroups. The results in patients with high disease activity are further supported by the results obtained at 52 weeks as well as 76 weeks in the responder analyses with more stringent response criteria. In addition a substantially increased likelihood of a treatment response has been shown for the subpopulation of patients with anti-dsDNA antibodies and low complement levels.

From a safety point of view, although the mechanism for hypersensitivity and infusion reactions is currently unknown, the SmPC has been appropriately strengthened and includes recommendations for premedication and proper handling of potential events should they occur.

Belimumab represents a novel concept to induce immunosuppression. Thus, uncertainty exists regarding the potential for development of malignancies, as well as other potential long-term risks such as increased risk of developing opportunistic infections, or PML. This emphasizes the need for a proper long-term follow up. This is addressed by a 5-year large post-marketing safety study which is part of the agreed RMP; in this study events of interest, including serious infections, opportunistic infections, and malignancies (including hematological malignancies) will be monitored. No increased risk of malignancy can at the current time be attributed to treatment with belimumab.

The Risk Management Plan includes infections as an identified risk. In addition to routine pharmacovigilance, the Applicant will evaluate data on infections reported from ongoing and future clinical trials; furthermore, a post-marketing safety study will be conducted to further evaluate the incidence of all-cause mortality and adverse events of special interest, which include serious infections and opportunistic infections. For the time being no additional measures are necessary to minimize and monitor risk of infection.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Benlysta as add-on therapy in adult patients with active autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy was favourable and therefore recommended the granting of the marketing authorisation.

1.2. Dificlir

Benefits

Beneficial effects

Fidaxomicin represents a novel class of antibacterials, the 18-membered macrocyclic antibacterial drugs. Due to its unique mechanism of action which is distinct from that of any other class of antimicrobials the potential of cross-resistance to other antibiotic classes is anticipated to be low. The relatively low absorption of fidaxomicin ensures that a high concentration in the entire intestinal tract is maintained after oral administration. Its concentrations in the stool largely exceed the MIC of *C difficile* (up to 5 000 x MIC_{90} for *C. difficile*). In combination with the narrow spectrum of fidaxomicin and its main metabolite directed primarily against Clostridium species, an in vitro demonstrated anti-spore activity and the significant post-antibiotic effect, these features are beneficial characteristics for a drug in the applied indication CDI.

The non-inferiority of fidaxomicin compared to orally administrated vancomycin was demonstrated in two randomized double-blind controlled phase 3 studies in patients with mild to moderately severe *C. difficile* infection. The primary efficacy variable was clinical cure at end of therapy which was achieved for 92% in the fidaxomicin group and in 90% in the vancomycin group, in the PP population (Difference 1.7; 95% CI -1.7 – 5.3). Superiority was shown for secondary endpoints, recurrence rate (14% vs. 26%) and global cure rate (76% vs. 64%) for fidaxomicin and vancomycin, respectively (mITT-population), within 30 days after discontinuation of treatment. These results are considered highly clinically relevant, since recurrence of CDI is an acknowledged challenge with currently available treatments. The reduction in recurrences compared to vancomycin was mainly attributed to fewer recurrences the first two weeks after EOT, thus fidaxomicin appears to be associated with lower rate of relapses (likely with the same strain) while late recurrences (likely re-infection with a new strain) were equally common in both treatment groups. The recurrence rates within 30 days post-treatment were consistently significantly higher in the vancomycin groups compared to the fidaxomicin groups in both the PP and mITT populations. Subgroup analyses indicated consistent numerical superior outcome for fidaxomicin treated patients also in subgroups generally associated with inferior cure rates, including severe disease (as judged by the investigator or using ESCMID criteria), high age, prior episode of CDI, concomitant systemic antibiotic and inpatient status. Also global cure rates were consistently more favourable for the fidaxomicin treated patients. Global cure is considered a crucial endpoint since this endpoint may be considered most meaningful for the patient, taking the high recurrence rates after current available therapeutic options into account (20 to 30% recurrence rates have been reported after initial successful treatment with vancomycin or metronidazole).

The studied patient population seems to be generally representative for the target population, including a high number of elderly patients with almost 50% of patients ≥ 65 years and approximately 65% being hospitalised and a sufficient number of patients infected with the hypervirulent BI/027 strain (approximately 25%). While study 03 only enrolled patients from North America approximately 40% of patients included in study 04 were from European sites. Gender or ethnicity did not have an impact on the clinical response.

Uncertainty in the knowledge about the beneficial effects

More than 70% of included patients were considered by the investigators to have moderate to severe infection, but there is a lack of validated severity scoring index systems. Patients were generally comparable between treatment groups for reported baseline characteristics. However, data from several important subgroups of patients, such as patients with pseudomembranous colitis, patients with multiple recurrences of CDI, patients with IBD and patients with impaired renal and impaired hepatic function, are missing, which is addressed in the SmPC and in the RMP.

Patients with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months) were excluded from the studies. This group of patients currently constitutes a real clinical challenge and there is an urgent need for improved treatment alternatives leading to sustained cure. In addition, no data on repeated treatment with fidaxomicin have been presented. The Applicant has committed to perform a post-authorisation study in patients receiving repeated treatment with fidaxomicin, which is addressed in the RMP.

Risks

Unfavourable effects

Fidaxomicin is an NCE and the first representative in this novel antibacterial class of macrocycles, thus no clinical experience of this or similar drugs is available. The current safety data-base may be

considered very small and consists of a total of 660 patients with mild to moderately severe *C. difficile* associated diarrhoea treated up to 10 days with fidaxomicin.

The clinical studies indicate that fidaxomicin is well tolerated and has a safety profile in line with that of orally administered vancomycin. The most frequent drug-related TEAEs in the pooled analysis were nausea, hypokalaemia, headache, vomiting and abdominal pain. The safety profile in general and considering drug-related events was very similar between the treatment groups and between studies.

Serious events including death were reported in both phase 3 studies, however these appear to be consistent with the clinical condition of individual patients and were reported by a similar rate in the two treatment arms. The highest frequency of serious adverse events (SAEs) was reported in the SOC Infections and Infestations. The most frequent preferred terms in the pooled analysis were pneumonia, *C. difficile* colitis, sepsis and respiratory failure. The SAEs neutropenia, blood uric acid increased, hypophosphataemia and gastrointestinal haemorrhage occurred more commonly in the fidaxomicin group. Although confounding factors such as underlying conditions and concomitant medications seemed to at least partly contribute to these imbalances between treatment groups, these adverse events should be closely monitored and cumulatively reported in future PSURs.

There was an imbalance in significant changes in liver function tests parameters between treatment groups, with higher number of patients in the fidaxomicin groups presenting increased transaminases, mainly driven by study 04. The majority were associated with underlying or concomitant conditions and the LFTs were basically recovered at the end of the investigation period. Five subjects in each group had a reported SAE involving abnormal LFTs. There did not appear to be a correlation with plasma concentrations of fidaxomicin.

Uncertainty in the knowledge about the unfavourable effects

Safety assessment in acutely-ill patients with severe diarrhoea and a significant degree of co-morbidity is complex and complicated by the fact that the disease itself can induce reactions such as electrolyte disturbances, nausea, abdominal pain, gastrointestinal bleeding and other symptoms.

Patients with fulminant colitis and patients with inflammatory bowel diseases were excluded from the studies. As absorption from the gastrointestinal tract may be increased in these patients, the safety profile may be different in these patient populations, which is addressed in the RMP as well as in the Product Information. Exposure is also increased in patients with hepatic impairment and in patients with co-administration of P-gp inhibitors. Caution should be advised in patients with moderate to severe hepatic impairment and co-administration of potent P-gp inhibitors should be avoided.

In addition the present uncertainty regarding plasma levels in CDI patients have implications for the evaluation of exposure margins.

Fidaxomicin is a new chemical entity without previous experience in clinical practice and although absorption may be considered relatively low, it cannot be ruled out that levels of systemic exposure may lead to potential safety effects, especially in patients with damaged intestinal mucosa, such as patients with severe CDI and patients with inflammatory intestinal diseases. The presented safety data base is considered very small for an NCE and safety data are currently missing in patients subjected to repeated use of fidaxomicin. Also potential emergence of resistance in the clinical setting is unknown which is addressed in the RMP and in the SmPC. Information on repeated use of fidaxomicin is missing which is addressed in the RMP. The applicant has committed to perform a post-approval study in patients receiving repeated use of fidaxomicin as well as performing a post marketing non-interventional study to further assess the use of fidaxomicin in standard clinical practice. Due to the limited clinical experience of this novel drug, monitoring of adverse events concerning laboratory

parameters including haematological and hepatic data should be performed with cumulative reporting in future PSURs.

Benefit Risk Balance

Importance of favourable and unfavourable effects

The fact that fidaxomicin belongs to a novel antibiotic class is considered important from an antibiotic resistance perspective, limiting the risks for cross-resistance. A limited disruption on the normal intestinal flora as well as activity against *C. difficile* spores is considered valuable, since it may contribute to lesser frequency of recurrences. The non-inferiority to vancomycin in clinical cure rates and in particular the superiority in global cure rates, in particular concerning relapses, is very promising, considering the major negative consequences of repeated recurrences, both for the society and for the individual subject.

Data from the current studies indicate that fidaxomicin is well tolerated with a safety profile in line with vancomycin. However, there are several uncertainties remaining, related to potentially increased systemic exposure in patients with impaired hepatic function and in patients with increased absorption of the drug (either due to damage intestinal mucosa or during co-administration of P-gp inhibitors), as well to lack of data in important groups of patients. These uncertainties are stated in the Product information and adequately addressed in the RMP.

Benefit-risk balance

The severity of the disease and the medical need for new agents to treat CDI should be considered along with the unknown risks of this novel drug especially related to seriously ill patients with severely damaged intestinal mucosa. At the present stage, the benefit – risk relationship for fidaxomicin in the treatment of CDI is considered to be favourable.

Discussion on the Benefit Risk Balance

The benefit-risk for fidaxomicin should be weighed to that of currently available treatment options for CDI, vancomycin and metronidazole. Both these drugs are hampered by several drawbacks. CDI is a significant and increasing medical problem, and an effective and safe treatment alternative is urgently needed. The current data base for fidaxomicin may be considered sufficiently demonstrating the benefits of fidaxomicin in the sought indication, provided that adequate post-marketing activities, as guided in the RMP, are adhered to.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Dificlir indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) (see section 5.1) is favourable and therefore recommends the granting of the marketing authorisation.

1.3. Edarbi

Benefits

Beneficial effects

Azilsartan medoxomil is a selective AT1 receptor blocker (ARB) indicated for the treatment of essential hypertension. Significant blood pressure reduction versus placebo in the *short-term* trials of 6 weeks was demonstrated for the whole range of azilsartan medoxomil formulations of 20mg, 40mg and 80 mg in patients with mild to moderate uncomplicated essential hypertension (-12.2 mmHg to -14.6 mmHg 24h SBP). The 40 mg and the 80 mg azilsartan medoxomil doses were superior to (maximal dose) valsartan 320mg (-10.2 mmHg, $p<0.001$) and the 80 mg dose was superior compared to a maximal dose of olmesartan (-11.7 mmHg versus -12.6 mmHg 24h SBP, $p=0.038$) on ABPM, clinical SBP and responder rates (56.6-57.8% AZI 80 vs 48.7-53.2% OLM, $p=0.035$). A more severe hypertensive patients group was included in the open-label phase conform with the inclusion criteria and sufficient numbers of patients were analyzed to assess antihypertensive efficacy.

Consistent efficacy was found across subgroups, including patients with renal insufficiency, except for the age group of > 75 years of age and in the black population versus placebo. A lower, but still significant response for the black subjects was also demonstrated in the clinical study including only a black population. This is known from other ARBs and ACE-inhibitors and possibly due to the higher prevalence of low-renin states in black hypertensive patients.

For the *long-term* (24 weeks) comparative studies, significant more systolic blood pressure reduction was demonstrated for both doses of azilsartan medoxomil 40 and 80 mg compared to valsartan (24h SBP –14.9, -15.3 and -11.3 mmHg, resp. ($p<0.001$ vs. valsartan) and ramipril (clinical SBP for 40 mg, 80 mg dose and ramipril is -20.6, -21.4 and -12.2 mmHg, resp. ($p<0.001$ vs. ramipril)). Reduction in diastolic blood pressure and responder rates were consistent with these results. Consistent findings were observed for the blood pressure lowering across subgroups.

In the *co-administration* studies, both the 40 mg and 80 mg azilsartan medoxomil demonstrated additional efficacy when combined with amlodipine and chlorthalidone (-24.8, -24.5 vs -13.6 (AML) and -31.7, -31.3 vs -15.9 (CLD) mmHg 24h SBP, respectively).

The long-term *open-label* studies demonstrated that azilsartan medoxomil efficacy was maintained during the entire study period. Addition of CLD, amlodipine or HCT resulted in additional blood pressure lowering in these studies. Maintenance of efficacy was further demonstrated with the reversal phase in study 491-016 where treatment continuation was associated with significant larger blood pressure reduction compared to patients assigned to placebo. In addition, a post-hoc analysis demonstrated additional efficacy of the 80 mg dose in non-responders to 40 mg of approximately 5 mmHg SBP.

Patients with pre-existent cardiovascular events/co-morbidities (n=378) were allowed in the studies, and showed similar antihypertensive efficacy to the overall population.

Uncertainty in the knowledge about the beneficial effects

Twenty-four hour blood pressure lowering efficacy maintenance (trough-to-peak ratio) was not different for azilsartan medoxomil compared to olmesartan (0.952 and 0.771 for 80 mg azilsartan medoxomil and 0.915 and 0.892 for olmesartan 20 mg during 24h in 2 studies) and this stronger effect of azilsartan medoxomil does not appear related to its PK properties, but possibly to a slower dissociation of the AT1 receptor (see also non-clinical section).

Only limited data were obtained in more complex patients, i.e. patients with co-morbidity such as heart failure and diabetes mellitus, and the very elderly. Less efficacy in the > 75 years of age subgroup was demonstrated for azilsartan medoxomil versus comparator and placebo in the short and long-term studies with wide confidence interval due to limited number of patients. High risk patients (according to ESC (clinical SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg, clinical SBP > 160 mm Hg and DBP < 70 mm Hg, metabolic syndrome, ≥ 3 CV high risk factors, subclinical organ damage, CV/renal disease, or diabetes) and SCORE classification (≥ 5% risk of CV death within a 10-year period)) showed similar efficacy as to the overall population.

Beneficial effects of azilsartan medoxomil on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Risks

Unfavourable effects

An adequate number of patients treated with azilsartan medoxomil have been evaluated compared to placebo and active comparators. Furthermore sufficient numbers of patients have been included to evaluate long-term safety: 1704 for more than 26 weeks and 588 for more than 48 weeks.

The adverse events of dizziness, fatigue, headache, blood creatinine increased, hypotension, dizziness postural, and blood CK increased were consistently found during study drug treatment across the different controlled and open-label trials.

Adverse events of diarrhoea, dizziness, hypotension and fatigue are well known from other ARBs and appear to be dose-related as they occur most often in the highest dose group. In the placebo controlled studies incidences of these side effects were 0, 0.7 and 1.3% for placebo; 0.9, 1.9 and 2.3% for azilsartan medoxomil 40 mg; and 0.2, 0.4 and 1.1% for azilsartan medoxomil 80 mg, respectively. They may occur within a few weeks and are generally mild in nature. Only slightly more patients discontinued on azilsartan medoxomil than on placebo and generally, treatment was tolerated well. The incidence of serious adverse events was generally low.

A detailed description of renal adverse events showed that incidences were low and not much higher than for placebo. A dose-dependent relation for blood creatinine increase (or GFR decrease) may occur that was most pronounced in the long term studies: 1.1%, 3.4% and 3.1% for comparator, azilsartan medoxomil 40 and azilsartan medoxomil 80 mg. Increase in the level of serum creatinine is known to be associated with RAAS blockade and has been observed with other ARBs. The use of azilsartan medoxomil according to renal impairment showed no clear trend towards more adverse events, discontinuation due to adverse events or severe adverse events with increasing impairment of renal function.

Uncertainty in the knowledge about the unfavourable effects

The number of patients treated for more than 52 weeks is unknown, although approximately 588 patients were treated for 48 weeks or more.

In contrast to other ARBs an increase in uric acid increase was observed, in particular in the longer term. This could partly be explained by a reduction in GFR that fits with the potent AT1 antagonist effect. The increase in uric acid levels was not combined with an increased number of related adverse events such as gout and nephrolithiasis.

Some abnormalities in liver enzymes (ALT, AST and triglycerides) were noticed, but were not consistent for all trials and were of a similar level as for the comparators (valsartan, ramipril). Some detailed description has been provided.

There seems not to be a relation between study drug and the death cases that occurred, however, for one case this was uncertain, in particular because of lack of information.

Based on the data provided here, no trend towards a higher incidence of neoplasm or cancer could be observed, but incidences were very low and no conclusions can be drawn. A recent meta-analysis identified no increased risk with ARBs in contrast to previous publications. Laboratory adverse events related to blockade of the RAAS (creatinine, potassium, sodium, etc.) were increased during long-term treatment in these moderate and severe renal impaired patients. Conclusions regarding dose recommendation for the renally impaired patients cannot be made based on these results. Exposure to azilsartan medoxomil may be doubled in these patients (see pharmacokinetic section). More careful up-titration in patients with severe impairment has been recommended in the SmPC.

Clinical experience treating patients with any type of hepatic impairment is extremely limited. The applicant conducted one hepatic impairment study, which included 8 patients with mild and 8 patients with moderate hepatic impairment. In these patients a slight increase (1.3 to 1.5 fold) in azilsartan medoxomil exposure was observed but still adverse event patterns could be different due to an increased pharmacodynamic response. Severe hepatic impaired patients were not included in the

studies. Therefore caution is needed and a starting dose of 20 mg azilsartan medoxomil could be considered in subjects with mild and moderate hepatic impairment. The use of azilsartan medoxomil cannot be recommended in patients with severe hepatic impairment as reflected in the SmPC.

Although numbers of elderly were limited, typical adverse events associated with the more elderly are found such as hypotension and dizziness. However, these were similar between azilsartan medoxomil and comparator. Numbers of very elderly, diabetes mellitus, and heart failure or activated RAAS were more limited. Therefore, the safety profile of azilsartan medoxomil in these patients is not clearly established. The external validity for such patients is limited.

Benefit-risk balance

Importance of favourable and unfavourable effects

Antihypertensive treatment is indicated to reduce the risk for cardiovascular events. Reduction of blood pressure is directly associated with reduction of CV events. The choice of 24 hour ABPM systolic blood pressure as primary endpoint is considered appropriate. It provides an appropriate insight into blood pressure changes during everyday activities and is strongly recommended for the evaluation of new antihypertensive agents. In addition, the choice of clinical SBP at trough as the major secondary endpoint is important as the best evidence for association between blood pressure reduction and reduction of CV risk still comes from SBP.

Azilsartan medoxomil is a new ARB, belonging to a group of antihypertensives that has an established place in the treatment of hypertension. Its antihypertensive effects as demonstrated in the development programme are considered clinically relevant and at least comparable to other antihypertensive agents.

Beneficial effects of azilsartan medoxomil on mortality and cardiovascular morbidity and target organ damage are currently unknown.

The observed AE include mainly diarrhoea, hypotension, dizziness and fatigue and these are generally well tolerated. Laboratory abnormalities may occur, in particular increases in creatinine and serum potassium. This is similar to other ARBs and manageable in the tested population. Unexpected uric acid increase was observed which could be partly related to a reduced GFR.

Clinical experience in very elderly patients (> 75 years), patients with renal and hepatic impairment and high CV risk (heart failure, DM) is limited. Uncertainties still remain on the safety profile of azilsartan medoxomil and the dosing recommendations for these patients.

Benefit-risk balance

The balance between favourable and unfavourable effects of azilsartan medoxomil is considered positive. Its antihypertensive efficacy has been established in patients with uncomplicated mild to severe essential hypertension in dosages ranging from 20-80 mg. The 40 mg dose is considered an acceptable starting dose in these patients. The AE observed with azilsartan medoxomil are similar to those observed with other ARBs and appear to be dose-related. AEs may occur within a few weeks and are generally mild in nature.

Discussion on the benefit-risk balance

The overall benefit/risk of azilsartan medoxomil is considered positive for the indication: *"Treatment of essential hypertension in adults"*.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Edarbi in the treatment of essential hypertension in adults is favourable and therefore recommends the granting of the marketing authorisation.

1.4. Edurant

In European Union, Rilpivirine is the fourth representative of the Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) after nevirapine, efavirenz (EFV) and etravirine. The applicant applied for the indication in treatment of HIV-1 infection in antiretroviral (ARV) treatment-naïve adults. As such, according to current HIV treatment guidelines, it could be considered an alternative to EFV as the first choice NNRTI agent in first line ARV regimens.

Benefits

Beneficial effects

The beneficial virological effects of RPV is clearly demonstrated in two pivotal phase III randomized trials, comparing RPV to EFV, both in combination with 2 NRTIs, in treatment-naïve HIV-1 infected adults. NRTI backbones used were tenofovir/FTC (major part), abacavir/lamivudine or zidovudine/lamuvidine. Both studies demonstrated non-inferiority of RPV to EFV; at 48 weeks follow-up, the overall response rate (< 50 copies/mL) for pooled results was 84% and 82% for RPV and EFV respectively. Such response rates are similar to previous studies with EFV.

RPV has a favourable tolerability profile compared to EFV, as relatively common skin disorders and neuro-psychiatric side effects were reported less frequently.

Uncertainty in the knowledge about the beneficial effects

The beneficial effects in individuals with high baseline viral load (and low CD4 T-cell counts, often associated with high viral loads) are questionable. Post-hoc analyses stratified for baseline viral load (≤100,000 versus >100,000 copies/ml) for the overall population and the tenofovir/emtricitabine subset confirmed the trend towards lower efficacy in patients with high baseline viral load (77% with TCM278 versus 81% with EFV) whereas efficacy was comparable (numerically higher) for patients with baseline viral load ≤100,000 copies/ml (90% versus 84%). Although response rate appears lower in patients with CD4 count < 50 cells/□l, numbers are too low to draw conclusions on the impact of low CD4 count per se.

In phase 2b three doses of RPV were tested: 25 mg, 75 mg and 150 mg. There was not an obvious difference in overall efficacy between doses, although a trend for higher incidence of virological failure with the lowest dose was noted. Due to concerns of QT-effects with the higher doses in a thorough QT study, the lowest dose was chosen for phase 3. Within phase 3, using the 25 mg dose, outcomes were associated to RPV exposure (using population PK data); the response rate was significantly lower for RPV patients belonging to AUC quartile 1 compared to AUC quartile 3. Hence, the exposure achieved with the 25 mg dose is just at the edge , or slightly below the Emax of RPV - which gives efficacy problems mainly in patients with a high baseline viral load, but less so in patients with lower viral loads. Hence, any concomitant drugs that would lower the RPV exposure, as well as intake an intake in fasted state, is likely related to a risk of lower efficacy, and the development of resistance. It is uncertain whether these issues will be handled as carefully in clinical practice as within a well controlled trial. It is crucial that the need for correct intake (fed state) and the risk associated with certain interacting drugs is emphasized in the SmPC. However, the later restrictions might be difficult to handle in clinical and daily practice, with the potential risk of lower virologic response and emergence of resistance. Whether restrictions like low baseline viral load and dosing instructions can be met in daily clinical practice or that the somewhat suboptimal dose is more fragile here than within clinical trials, needs to be confirmed by the drug utilisation study and subsequent PSURs.

It remains to be seen whether an increased dose of this order would make a substantial difference in the numbers of virological failure in those patients with a high baseline viral load. The rather low potency of rilpivirine might be the main obstacle with regards the risk of resistance development (1.2 $\log_{10}$ reduction in monotherapy, regardless of dose used).

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and studies are ongoing in patients switching from other therapies to RPV. In addition to this, the applicant is requested to perform a drug interaction study with efavirenz and 50 mg rilpivirine dose as metabolic induction by efavirenz holds for quite some time. Further lowering exposure of the 25 mg dose rilpivirine might increase the risk of virological failure.

Patients with a number of baseline HIV resistance associated mutations, an estimated glomerular filtration rate < 50 ml/min, AIDS defining illness or any significant co-existing illness were excluded from the phase III trials.

The number of HIV patients aged over 65 years treated with RPV is too low to draw any conclusions for this subgroup. However, based on the mechanism of action there is no reason to expect a less beneficial effect of RPV among the elderly or those with co morbidity including renal insufficiency.

There are currently no data available from clinical studies with RPV to support the combination of RPV with other antiretroviral agents than tenofovir/emtricitabine, abacavir/lamivudine or zidovudine/lamivudine.

Finally, the beneficial effect (non-inferiority of RPV to EFV) has been demonstrated in the phase III trials for 48 weeks of follow-up. The 96-weeks data of these trials are expected to become available by 1Q 2012.

Risks

Unfavourable effects

As with all ARVs, once there is virological failure there is a risk of emerging resistance. The extensiveness of this determines the available alternative ARVs left for 2nd line treatment.

In the pivotal studies there was overall a 2-fold risk for virological failure for RPV-treated patients compared to those treated with for EFV; 10.5% versus 5.7%. About half of the patients with virological failure (both with RPV and EFV) developed resistance associated mutations; thus RPV was also associated with a 2-fold higher risk to develop resistance. Moreover, RPV resistance was associated with cross-resistance to the 2nd line NNRTI (etravirine) whereas in case of resistance to EFV, susceptibility to etravirine remained. In addition, patients failing RPV therapy more frequently developed resistance to the NRTI backbone (particularly emtricitabine/lamivudine) than did patients failing with efavirenz.

Post-hoc analyses demonstrated that this increased risk of virologic failure was driven by patients with high baseline viral load (i.e >100,000 copies/ml) , 15% with RPV versus 6% with EFV, whereas virologic failure rates were comparably low for patients with low baseline viral load, 3.8% versus 3.3%, regardless of NRTI backbone used. Hence, for the high viral load strata, the risk for emerging resistance (NNRTI and/or NRTI) was 3-4 times higher for those treated with RPV compared to those treated with EFV. In contrast, the number of patients developing resistance was low and similar to that seen for efavirenz-treated patients within the low viral load strata.

The most frequently reported treatment-related AEs in the patients treated with RPV were nausea, dizziness, abnormal dreams and headache. These AEs were mild and occurred less frequently with RPV than with EFV.

Tenofovir carries a, dose dependent, risk for renal tubular toxicity which in turn causes phosphate loss with bone loss as perhaps the most important outcome measure. Post-hoc analyses of the optional DEXA sub study within the phase 3 studies showed that there was no difference in bone parameters for rilpivirine and EFV at week 96, regardless of NRTI backbone. Also, rates of hypophosphatemia were quite the same between treatment arms. Therefore, there are no suggestions for a possible additive/synergistic risk for tubular toxicity when rilpivirine is given in combination with tenofovir.

Uncertainty in the knowledge about the unfavourable effects

An extensive list of NNRTI-associated mutations (n= 39) constituted exclusion criteria in both phase 2b and phase 3 (around 10% of all screening failures). Many of these NNRTI-associated mutations were quite infrequent though, and were neither seen in the in vitro resistance profile of RPV, nor in patients failing RPV therapy in the trials. In the final analyses of all data a list of 15 RPV-associated mutations is proposed to constitute those baseline mutations precluding RPV therapy in treatment naïve patients. This list covers the majority of the population not included in the trials, and the analyses behind it are endorsed. The combined frequency of these 15 mutations is high enough in untreated patients to

request that resistance testing should be done prior to the use of RPV. This is reflected in the indication: as with other antiretroviral medicinal products, genotypic resistance testing should guide the use of rilpivirine and cross reference is made to the relevant sections 4.4 and 5.1.

To perform resistance testing prior to the use of RPV is in line with the general recommendation in Europe - which implies that a baseline resistance testing should be done prior to starting HIV therapy (Vandamme et al, 2011). The other mutations used as exclusion criteria, not included in this list, were deselected by the company after final analyses of pre-clinical and clinical data; they were not found to affect activity in vitro and were not seen in any significant numbers in those failing RPV. Although they were formally not properly studied in vivo, the impact in response rates of the phase 3 studies would not have been significantly affected by their presence in the list of exclusion criteria. Future follow-up of resistance should be provided according to the proposed pharmacovigilance measures and the correctness of associated mutations should be confirmed.

In a thorough QT-study a somewhat unexpected QTc increase above the threshold (just above 10 ms for female subjects) was seen at doses 75 mg or higher. As consequence any risk factor for QT prolongation was an exclusion criterion in the phase III trials giving an uncertainty about the safety of RPV in individuals with such risk factors. However, no difference in QTc increase was seen for the 75 mg dose compared to and efavirenz in the phase 2b study (using common 12-lead ECGs). Also no significant QTc change was noted in an interaction study with RPV 150 mg qd in combination with darunavir/r, which further doubles the exposure. Therefore, the clinical relevance of the QT-prolongation observed at a dose of 75 mg is currently unclear.

Furthermore, post-hoc analyses showed a low incidence for patients with risk of QTc prolongation at screening to phase 3, and observed risk factors were of limited clinical relevance. Therefore, as the 25 mg dose was not associated with QTc interval prolongation, no special warnings are required for the moment. A warning on QT prolongation with supratherapeutic dose (75 mg and higher) was included in section 4.4 of the SmPC.

The applicant could not provide additional safety data on parameters adequate for monitoring tubular injury (urine-protein, urine-β2-microglobulin etc), as these were not collected during the studies. However, other available data do not point toward tubular toxicity with rilpivirine. Still, given the fact that tenofovir exposure is highly dependent on renal clearance the effect of rilpivirine on renal clearance and creatinine levels is reflected in sections 4.2 and 4.8 of the SmPC, as well that rilpivirine was only studied in patients with normal renal function.

Benefit Risk Balance

Importance of favourable and unfavourable effects

As the targeted indication is the treatment of HIV-1 infection in ARV-naïve individuals, both tolerability and efficacy of the ARV regimen are of high importance; this is the start of a potential life-long treatment. In this light, the noted better tolerability of RPV compared to the golden standard EFV, is considered of clinical relevance. Also the qd dosage and low pill burden are advantages that can make it easier for patients to comply with therapy.

A prerequisite of the ARV regimen is its virological potency. Any inability to suppress HIV replication is considered of clinical concern as this may lead to resistance hampering 2nd line ARV treatment options. Virological failure due to resistance should therefore be considered of greater clinical relevance than the tolerability of the regimen.

Benefit-risk balance

Overall, it can be concluded that RPV was non-inferior to the active comparator EFV with respect to the most relevant clinical endpoint (<50 copies/mL). The potential extra benefit over EFV relies in a better tolerability, all be it predominantly the first four weeks of treatment, and the patients convenience having one tablet, once daily as ARV regimen.

This benefit, together with the non-inferior efficacy, should be balanced against an overall 2-fold higher risk of RPV for developing virological failure and emerging resistance of which the latter has greater clinical consequences, as resistance to RPV was also more frequently associated with resistance development to the backbone NRTIs.

In the pivotal phase III studies, the overall risk of emergence of resistance appeared to be about 6% versus 3% for RPV and EFV, respectively. In further analyses it was shown that, the increased risk of emerging resistance with TCM278 is driven by patients with high baseline viral load (>100,000 copies/ml); these patients show lower virologic response rates and higher rates of virologic failure compared to EFV. On the other hand, for patients with baseline viral load ≤100,000 copies/ml TCM278 showed numerically higher response rate and a low risk of emerging resistance and in the same order of magnitude as observed for EFV. It can be expected that the ongoing studies up to 96 weeks will confirm the observed comparative efficacy and safety profiles of RPV.

Based on these arguments the limited benefit of better tolerability does not weigh against the higher risk for emerging resistance for treatment naïve patients at large - the risk of failure and its consequences are not acceptable for patients with a high baseline viral load, taking into account the performance of other available first line options for such patients. Therefore, the CHMP considers that the benefits outweigh the risks when RPV is restricted to patients with low baseline viral load.

Since the 25 mg dose is at the edge of being suboptimal, it is crucial that the exposure is not lowered (concomitant drugs, need for intake in fed state); there is always a risk that these issues are handled less strict in clinical practice than within a clinical trial, where everything is closely monitored. This risk was emphasized in the respective sections of the SmPC. Therapy should be guided by resistance testing as it is considered current good clinical practice in line with the general recommendation according to updated European treatment guidelines.

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and new studies are on going on use in patients switching from other therapies to RPV.

Discussion on the Benefit Risk Balance

From an individual patient perspective, the reason for judging an ARV agent to be abandoned from the 1st line regimen, either intolerability or insufficient virological effect, is not so relevant as long as alternate future, 2nd line, options are still available. Rilpivirine presents a higher risk for emerging resistance limiting 2nd line options, although nevertheless available 2nd line options in general still remain. However, whenever possible, avoidance of emerging resistance is considered more critical than tolerability.

The restriction of the indication to patients with low baseline viral load resolves the major concern on increased risk of emerging resistance compared to efavirenz. As mentioned above although the potential consequences of developing resistance are of greater concern with RPV given the potential loss of treatment options, the absolute risk is low and available 2nd line options still remain. Interaction with drugs that lower RPV exposure is contraindicated given the potential lower efficacy and

subsequent emergence of resistance and RPV must be taken in fed state. Within these restrictions, in patients with low viral load the risks are outweighted by the benefits of RPV showing a comparable high virologic response rate with a better tolerability profile to efavirenz and a favourable once-daily dosing regimen.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Edurant "in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in antiretroviral treatment naïve adult patients with a viral load ≤ 100,000 HIV 1 RNA copies/ml. This indication is based on week 48 safety and efficacy analyses from two randomised, double blind, controlled, Phase III trials in treatment naïve patients and week 96 safety and efficacy analyses from a Phase IIb trial in treatment naïve patients (see section 5.1). As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EDURANT (see sections 4.4 and 5.1)." is favourable and therefore recommends the granting of the marketing authorisation.

1.5. Eliquis

Benefits

Beneficial effects

In Total Hip Replacement (THR) study (CV185035), apixaban demonstrated a significant superiority to enoxaparin for the primary efficacy endpoint (composite endpoint of all VTE/all-cause death). The point estimate was 1.39% vs. 3.86%; p < 0.0001, relative risk reduction [RRR]: 64% - 95% CI = 0.22, 0.54). More importantly, this superiority was demonstrated also on major VTE (proximal DVT, non-fatal PE and VTE-related death). Reported event rates were 0.45% vs. 1.14%; p=0.0107, RRR: 60% - 95% CI = 0.15, 0.80. Results of the main secondary endpoints are mainly driven by the favorable results of proximal DVT (7 vs 20 cases in the apixaban and enoxaparin groups respectively). There is a reduction in the events of non-fatal PE (apixaban(2) and enoxaparin(5)) but there was one case of VTE-related death in the apixaban arm. In the follow-up period, PE and symptomatic proximal DVT were recorded in higher numbers in the enoxaparin (4 and 3 cases respectively) compared to none in the apixaban group. A benefit of apixaban in THR over the standard comparator was considered adequately proven.

In Total Knee Replacement (TKR) study **(**CV185047), superiority of apixaban was also shown over enoxaparin in the primary endpoint (15.06% vs. 24.37%; 2-sided p-value <0.0001, RRR: 38%; 95% CI = 0.51, 0.74) as well as the secondary endpoint (1.09% vs. 2.17%; p-value=0.0373, RRR: 50% - 95% CI = 0.26, 0.97). This superiority is not only driven by the incidence of distal DVTs (14.52 % and 23.9% respectively), but also the clinically relevant proximal DVT events (0.76% and 2.17% respectively).

Uncertainty in the knowledge about the beneficial effects

The superiority demonstrated by apixaban over enoxaparin in TKR was associated with an increase in PE (3 vs 0 respectively) and one VTE-related death versus no events with enoxaparin. Results of the follow-up period show one additional case of VTE-related death, 2 cases of PE and 2 cases of symptomatic proximal VTE in apixaban arm versus 0, one and one case for enoxaparin respectively.

In the TKR supportive US study, in which enoxaparin was administered as 30 mg BID, non-inferiority of apixaban against enoxaparin was not reached. Importantly, here also an increase in PE in the apixaban group (n=14; 0.88%) was observed compared to the enoxaparin group (n=7; 0.44%).

There was an increase in VTE-related deaths in the apixaban arm in TKR (1 and 2 cases in the EU and US studies respectively) compared to none with enoxaparin. Three major issues were explored as possible contributory factors to the higher incidence of events above described: patient characteristics, timing of initiation of apixaban and the posology. Patient characteristics (risk factors, compliance, co-administration of other drugs) were balanced and where not considered by the CHMP as influential. Geographical location/medical practice probably had an effect on the higher incidence of PE reported in the US/Canada study compared to the EU study, but could not explain the higher incidence of PE in the apixaban compared to enoxaparin in the same study. Duration of hospital stay was also longer in the EU study than in the US, with better results in the EU study, precluding the duration of hospital stay to be of importance in the current assessment. The duration of thromboprophylaxis used in the TKR studies are in line with previously performed studies and CHMP guideline. However, in some patients an extension of prophylaxis beyond 14 days could have been beneficial to prevent the cases of PE reported in the follow up period. This is also in line with the most recent ACCP guideline (2008) and applies also to all other antithrombotics. The time of initiation of apixaban is more delayed than other anti-coagulants. Presented data suggest that for both apixaban and enoxaparin delayed initiation of administration is associated with higher risk for total VTE, but not major VTE. The advantages of delayed initiation should probably be individually balanced against the VTE risk per agent used.

In conclusion, the CHMP was of the opinion that this increase of PE events was probably chance findings. This can be further supported by the observation that this increase of PE was isolated, without a comparable increase in the incidence of DVT. This is not a likely event, considering that most PE events originate from the leg veins. In addition, the reported incidence of PE in the enoxaparin arm in the EU study was lower (0.07%) than the US study (0.44%), which is counterintuitive, considering the doses of enoxaparin used.

Risks

Unfavourable effects

Available safety information related to apixaban 2.5 mg BID in the indication of VTEp was considered adequate (n=5,924) to characterize the safety profile of apixaban in this indication. The duration of exposure is also relevant to the indication.

Overall, results indicate that the adverse events and treatment emergent adverse events profile of apixaban was similar to that of enoxaparin.

The overall frequency of SAEs with onset during the treatment period and the follow-up period in the four pooled VTEp studies was similar in the apixaban and enoxaparin groups (392 [6.6%] and 396 [6.7%], respectively in the treatment period and in the follow-up period: 46 [0.8%] and 49 [0.9%] respectively. No SAE was reported for > 1% of subjects in either treatment group. The most frequently reported serious adverse events were deep vein thrombosis and pulmonary embolism.

Overall event rates for deaths were low in both treatment groups with only numerical differences between treatment groups during the treatment period (apixaban 10/5924 [0.17%], enoxaparin 7/5904 [0.12%]). The event rates for death in the apixaban group were consistent with rates reported during the treatment period in published reports of enoxaparin-controlled joint replacement studies (ranging from 0 to 0.3%).

Fatal PE was reported by the investigators for 5 (0.08%) subjects in the apixaban group and 1 (0.02%) subject in the enoxaparin group. Of these deaths, 4 events in the apixaban group and 1 event in the enoxaparin group were confirmed by adjudication.

The rate of death related to other causes was comparable between the treatment groups during the treatment period (apixaban 5, enoxaparin 6) and the follow-up period [apixaban 3 and enoxaparin 2].

There was a comparable risk of bleeding during both the treatment and the follow-up periods in the two pivotal studies between apixaban and enoxaparin administered in the lower dose of 40 mg QD, with major bleeding events slightly higher in the apixaban group in the THR study (0.82% vs 0.68%) and slightly lower in the TKR (0.6% vs 0.98%). In study CV185034, in which enoxaparin was administered as 30 mg BID a trend of lower risk of major bleeding was observed in favor of apixaban (adjusted difference of event rates -0.81%; p: 0.0533) and a significant reduction in the risk of the composite of major/clinically relevant non major bleeding (-1.46%; p=0.0338). Two fatal bleeding cases were reported in the enoxaparin group. The bleeding profile of apixaban appears to be better compared to enoxaparin in the TKR studies.

No clinically meaningful differences were noted in the frequencies of clinical laboratory test results for the apixaban and enoxaparin groups in any of the analysis periods.

No clinically relevant differences were noted in the event rates for bleeding between apixaban and enoxaparin groups within patients subgroups. Results suggest a comparable bleeding risk of co-administration of apixaban with NSAIDs compared to enoxaparin, sometimes even more favourable.

The rate of discontinuation due to AEs from the clinical studies was comparable between the treatment groups in the 4 studies (apixaban 200 [3.4%], enoxaparin 217 [3.7%]), with DVT and PE as the most common AEs leading to discontinuation.

Uncertainty in the knowledge about the unfavourable effects

Analysis of clinical and pre-clinical data did not support a hepatotoxic potential of apixaban. Actual representation of patients with different degrees of hepatic impairment in the current studies was not known, but patients with elevated liver enzymes were excluded in the clinical trials. This was clearly identified in the SmPC together with the need to measure ALT before administration. The incidence of concurrent elevations of ALT > 3 x ULN and total bilirubin > 2 x ULN was numerically higher with apixaban (n=8) than that reported with enoxaparin (n=5), and causality was assessed as possible in 2 apixaban cases, one of them was fatal. The causality of the drug in this fatal case was possible, but the contribution of other concomitantly administered drugs could not be excluded. Data from four completed clinical studies in other indications (n=2547) revealed one case of ALT > 3 x ULN and total bilirubin > 2 x ULN, which can be confounded by multiple co-morbidities. Blinded data from ongoing studies suggested that apixaban is unlikely to be hepatotoxic.

"Transient elevation of liver tests" was included as an Identified Risk in the RMP, and "hepatotoxicity" will be closely monitored in the post marketing period.

Apixaban, clopidogrel and ASA were co-administered in clinical studies in patients with ACS. Results show an increased bleeding risk in these patients, particularly in elderly patients and patients with CrCl < 60 ml/min. These risks were reflected in the SmPC.

Routine monitoring of apixaban is not needed. However, in cases of overdose or emergency surgery, the commercially available Rotachrom assay can be used. This was reflected in the SmPC.

Further safety data from the completed/ongoing studies should be submitted to facilitate the assessment of the safety profile of apixaban.

Balance

Importance of favourable and unfavourable effects

In the indication of VTEp in THR, apixaban showed favourable results that were considered by the CHMP both statistically significant as well as clinically relevant compared to enoxaparin.

The risk of bleeding was considered comparable to that of enoxaparin, with a slightly higher number of major bleedings

In the indication VTEp in TKR, apixaban also showed favourable results against enoxaparin in the pivotal study. In the supportive study, non-inferiority NI against enoxaparin was not achieved. The favourable results in the pivotal study were considered more relevant to the EU population, in particular taking into account the dose of enoxaparin used.

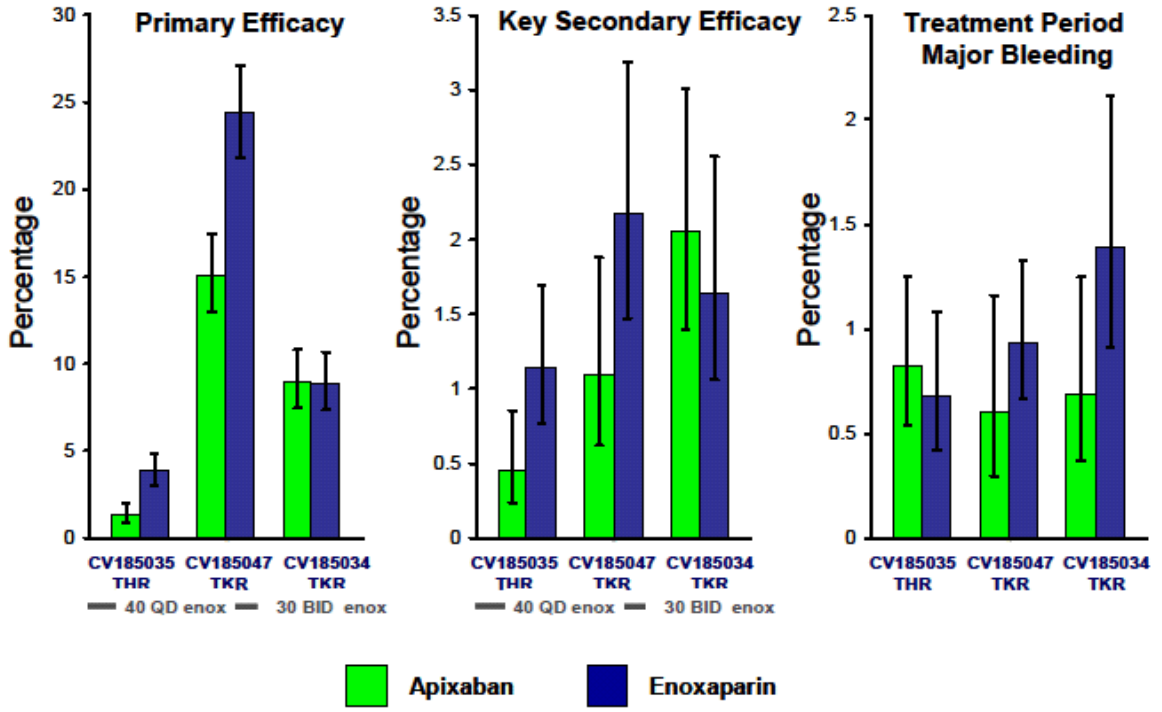
The higher incidence of PE and to a lesser extent VTE-related death in the apixaban group, could not be explained based on the explored patient characteristics or apixaban posology. Based on the current knowledge and compared to other studies, this higher PE incidence was considered by the CHMP to be probably a chance finding.

Bleeding risk appeared to be comparable if not better than enoxaparin. In the pivotal study, there were fewer major bleeding events in the apixaban group compared to enoxaparin.

Benefit-risk balance

Based on the above data, the beneficial effects of apixaban outweigh the unfavourable results in VTEp in both THR and TKR. Apixaban administration was associated with better efficacy in terms of superior reduction of the clinically relevant events of VTE compared with enoxaparin. This was accompanied with a comparable bleeding risk (main results are depicted in the figure below).

Apixaban Primary Efficacy, Key Secondary Efficacy, and Major Bleeding Event Rates in Subjects Undergoing Orthopedic Surgery (THR or TKR)



In case of VTEp in TKR, more cases of PE and fatal PE were recorded in the apixaban group. Further analysis did not show that patient characteristics or apixaban posology could have significantly contributed to these cases. Comparing the current results with those of other anti-coagulants, from previously conducted studies, this higher PE incidence could be considered by the CHMP to be a chance finding and this was reflected in the SmPC. Time of initiation of apixaban is delayed compared to other agents, which probably ensures a better bleeding profile, however this advice could be better individualized.

Current data did not point to a hepatotoxic potential for apixaban. Safety data from the ongoing studies should be submitted to facilitate further assessment of the safety profile for apixaban.

Discussion on the benefit-risk balance

Based on the above data, the beneficial effects of apixaban outweigh the unfavourable results in VTEp in both THR and TKR. Better efficacy in terms of superior reduction of the clinically relevant events of VTE compared with enoxaparin was demonstrated together with a comparable bleeding risk.

Time of initiation of apixaban is delayed compared to other agents, which probably ensures a better bleeding profile, however this advice could be better individualized.

In case of VTEp in TKR, more cases of PE and fatal PE were recorded in the apixaban group although not significantly attributed either to patient characteristics or apixaban posology. Comparing the current results with those of other anti-coagulants, this higher PE incidence was considered by the CHMP to be probably a chance finding and is reflected in the SmPC.

The SmPC currently contains adequate warnings for subgroups who may have higher risk for bleeding due to PK or PD interactions, in particular patients administered strong inhibitors of both CYP3A4 and P-gp, or platelet inhibitors, patients with moderate and severe renal impairment and elderly patients.

Safety data from the ongoing studies should be submitted to facilitate further assessment of the safety profile of apixaban.

In conclusion, the CHMP considered that the benefit/risk of apixaban is positive for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery".

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Eliquis in the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.

1.6. Eurartesim

Benefits

- Beneficial effects

Eurartesim meets the WHO recommendations for ACT since it comprises an artemisinin with a longer-acting partner drug. The two Phase 3 studies have demonstrated acceptable clinical efficacy of Eurartesim for the treatment of uncomplicated falciparum malaria in endemic areas.

- Uncertainty in the knowledge about the beneficial effects.

The possibility that dosing apart from food as recommended in the SmPC could have a negative impact on efficacy cannot be wholly dismissed. There is no appreciable effect of food on DHA absorption, which effects the early parasiticidal activity, but dosing Eurartesim with food greatly enhances piperaquine plasma levels. In this regard, the timing of the three daily doses in relation to food intake could not be discerned with confidence from the data collected during the Phase 3 clinical studies. While it is likely that the first doses were often taken on an empty stomach due to acute illness, the actual dosing conditions probably changed as clinical recovery ensued so that the second and third doses were more likely to have been taken with or close to a meal.

It is not possible to be sure that the efficacy observed in subjects resident in endemic areas would necessarily apply to returning EU travellers. EU travellers will comprise a mixture of ethnicities and a proportion of EU residents who spent much of their early life in endemic areas may still have some residual immunity to malaria but the majority will not. Plasma exposure to DHA and to PQP was at least numerically higher in healthy Asians vs. Caucasian subjects and was higher for DHA in female vs. male subjects on dosing after a light meal. However, the plasma levels of DHA are clearly very different between subjects with acute malaria and healthy subjects, which makes it difficult to draw any conclusions from these observations.

Risks

- Unfavourable effects

With the exception of effects on QTc intervals, the types and rates of unfavourable effects documented in the clinical studies were comparable between Eurartesim and the other ACTs that were evaluated.

- Uncertainty in the knowledge about the unfavourable effects

The current safety database is not sufficiently large to determine whether the QTc effect of Eurartesim will translate into arrhythmias and, if so, how frequently these may occur. However, the non-clinical data suggest that, despite the effect on QTc, the torsadogenic potential of Eurartesim may be low and there are currently no clinical data (from sponsored or published studies) that indicate a signal for clinically significant treatment-associated arrhythmias.

Benefit-risk balance

On current evidence, the risk-benefit balance of Eurartesim in treatment of uncomplicated falciparum malaria could be deemed favourable. This position takes into account the risk for cardiac side effects resulting from the pronounced Eurartesim-induced QTc-interval prolongation as demonstrated in the thorough QTc-study as well as in the pivotal clinical studies. It is considered that these safety concerns be sufficiently covered by the precautionary measures stated in the product literature.

Discussion on the benefit-risk balance

Malaria is a global problem with the greatest burden of disease and mortality occurring in tropical countries. Malaria is particularly dangerous in children under 5 years of age, pregnant women and previously unexposed visitors to endemic areas. *P. falciparum* is the most prevalent, treatment resistant form of malaria and is responsible for the severe and most deadly forms of the disease in children and adults.

A substantial number of EU residents are at risk of contracting malaria during leisure or business travel and migration. Eurartesim is an artemisinin-containing combination (ACT) that is recommended by the

2010 WHO guidelines for the treatment of malaria and is currently expected to be active against P. falciparum worldwide. In the two Phase 3 studies conducted in Asia (including areas with multiple drug-resistant falciparum strains) and in Africa, Eurartesim showed comparable efficacy to other ACT regimens in residents of endemic areas. However, based on pharmacokinetic data and plasma levels it cannot be ruled out that efficacy might not be quite as good as observed in the Phase 3 studies in subjects with no prior exposure to malaria and when Eurartesim is dosed apart from food.

The sponsored clinical studies indicated that, with the exception of the degree of effect on the QTc interval, the safety profile of Eurartesim was comparable to that of other ACTs. The non-clinical data and the available clinical data do not suggest that the effect on QTc is associated with serious cardiac arrhythmias, including torsades de pointes, but this possibility cannot be dismissed. Hence the SmPC and RMP take into consideration this possibility. In particular, the SmPC includes contraindications, warnings and precautions that are intended to minimise any risk for serious cardiac arrhythmias to occur.

Likewise as for other infective diseases, it is vital for the physician to have multiple treatment options. As such, Eurartesim might offer a useful alternative to current lead treatments available in Europe.

Overall, Eurartesim provides a Europe-wide alternative in the armamentarium of uncomplicated *P. falciparum* malaria treatment. The identified safety concerns are addressed in the Risk Management Plan (RMP) and Annex II.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Eurartesim in the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more is favourable and therefore recommends the granting of the marketing authorisation.

1.7. Eviplera

The fixed dose combination tablet combining tenofovir, emtricitabine and rilpivirine is the second ARV regimen containing one tablet once daily for treatment of HIV-1 in adults (the targeted indication). RPV is a new agent and the fourth representative of the Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) after nevirapine, efavirenz (EFV) and etravirine. As RPV is a new ARV, this assessment primarily focuses on the benefit-risk balance of this new agent in combination with TDF and FTC.

As bioequivalence has been demonstrated between the FDC tablet compared to the separate agents, this approach is considered appropriate for the risk-benefit assessment of the FDC tablet.

Benefits

Beneficial effects

The beneficial virological effects of RPV is clearly demonstrated in two pivotal phase III randomized trials, comparing RPV to EFV, both in combination with 2 NRTIs, in treatment-naïve HIV-1 infected adults. NRTI backbones used were tenofovir/FTC (major part), abacavir/lamivudine or zidovudine/lamuvidine. Both studies demonstrated non-inferiority of RPV to EFV; at 48 weeks follow-

up, the overall response rate (< 50 copies/mL) for pooled results was 84% and 82% for RPV and EFV respectively. Such response rates are similar to previous studies with EFV.

A bioequivalent study showed equivalence between the fixed dose combination tablet and the free combination of the individual mono-components. Since efficacy and safety have been established with the monocomponents the results are considered also applicable for the combination product.

RPV has a favourable tolerability profile compared to EFV, as relatively common skin disorders and neuro-psychiatric side effects were reported less frequently.

Uncertainty in the knowledge about the beneficial effects

The beneficial effects in individuals with high baseline viral load (and low CD4 T-cell counts, often associated with high viral loads) are questionable. Post-hoc analyses stratified for baseline viral load (≤100,000 versus >100,000 copies/ml) for the overall population and the tenofovir/emtricitabine subset confirmed the trend towards lower efficacy in patients with high baseline viral load (77% with TCM278 versus 81% with EFV) whereas efficacy was comparable (numerically higher) for patients with baseline viral load ≤100,000 copies/ml (90% versus 84%). Although response rate appears lower in patients with CD4 count < 50 cells/□l, numbers are too low to draw conclusions on the impact of low CD4 count.

In phase 2b three doses of RPV were tested: 25 mg, 75 mg and 150 mg. There was not an obvious difference in overall efficacy between doses, although a trend for higher incidence of virological failure with the lowest dose was noted. Due to concerns of QT-effects with the higher doses in a thorough QT study, the lowest dose was chosen for phase 3. Within phase 3, using the 25 mg dose, outcomes were associated to RPV exposure (using population PK data); the response rate was significantly lower for RPV patients belonging to AUC quartile 1 compared to AUC quartile 3. Hence, the exposure achieved with the 25 mg dose is just at the edge , or slightly below the Emax of RPV - which gives efficacy problems mainly in patients with a high baseline viral load, but less so in patients with lower viral loads. Hence, any concomitant drugs that would lower the RPV exposure, as well as intake an intake in fasted state, is likely related to a risk of lower efficacy, and the development of resistance. It is uncertain whether these issues will be handled as carefully in clinical practice as within a well controlled trial. It is crucial that the need for correct intake (fed state) and the risk associated with certain interacting drugs is emphasized in the SmPC. However, the later restrictions might be difficult to handle in clinical and daily practice, with the potential risk of lower virologic response and emergence of resistance. Whether restrictions like low baseline viral load and dosing instructions can be met in daily clinical practice or that the somewhat suboptimal dose is more fragile here than within clinical trials, needs to be confirmed by the drug utilisation study and subsequent PSURs.

It remains to be seen whether an increased dose of this order would make a substantial difference in the numbers of virological failure in those patients with a high baseline viral load. The rather low potency of rilpivirine might be the main obstacle with regards the risk of resistance development (1.2 log10 reduction in monotherapy, regardless of dose used).

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and studies are ongoing in patients switching from other therapies to RPV. In addition to this, the applicant is requested to perform a drug interaction study with efavirenz and 50 mg rilpivirine dose as metabolic induction by efavirenz holds for quite some time. Further lowering exposure of the 25 mg dose rilpivirine might increase the risk of virological failure.

Patients with a number of baseline HIV resistance associated mutations, an estimated glomerular filtration rate < 50 ml/min, AIDS defining illness or any significant co-existing illness were excluded from the phase III trials.

The number of HIV patients aged over 65 years treated with RPV is too low to draw any conclusions for this subgroup. However, based on the mechanism of action there is no reason to expect a less beneficial effect of RPV among the elderly or those with co morbidity including renal insufficiency.

Finally, the beneficial effect (non-inferiority of RPV to EFV) has been demonstrated in the phase III trials for 48 weeks of follow-up. The 96-weeks data of these trials are expected to become available by 1Q 2012.

Risks

Unfavourable effects

As with all ARVs, once there is virological failure there is a risk of emerging resistance. The extensiveness of this determines the available alternative ARVs left for 2nd line treatment.

In the pivotal studies there was overall a 2-fold risk for virological failure for RPV-treated patients compared to those treated with for EFV; 10.5% versus 5.7%. About half of the patients with virological failure (both with RPV and EFV) developed resistance associated mutations; thus RPV was also associated with a 2-fold higher risk to develop resistance. Moreover, RPV resistance was associated with cross-resistance to the 2nd line NNRTI (etravirine) whereas in case of resistance to EFV, susceptibility to etravirine remained. In addition, patients failing RPV therapy more frequently developed resistance to the NRTI backbone (particularly emtricitabine/lamivudine) than did patients failing with efavirenz.

Post-hoc analyses demonstrated that this increased risk of virologic failure was driven by patients with high baseline viral load (i.e >100,000 copies/ml) , 15% with RPV versus 6% with EFV, whereas virologic failure rates were comparably low for patients with low baseline viral load, 3.8% versus 3.3%, regardless of NRTI backbone used. Hence, for the high viral load strata, the risk for emerging resistance (NNRTI and/or NRTI) was 3-4 times higher for those treated with RPV compared to those treated with EFV. In contrast, the number of patients developing resistance was low and similar to that seen for efavirenz-treated patients within the low viral load strata.

The most frequently reported treatment-related AEs in the patients treated with RPV were nausea, dizziness, abnormal dreams and headache. These AEs were mild and occurred less frequently with RPV than with EFV.

Tenofovir carries a, dose dependent, risk for renal tubular toxicity which in turn causes phosphate loss with bone loss. Post-hoc analyses of the optional DEXA sub study within the phase 3 studies showed that there was no difference in bone parameters for rilpivirine and EFV at week 96, regardless of NRTI backbone. Also, rates of hypophosphatemia were quite the same between treatment arms. Therefore, there are no suggestions for a possible additive/synergistic risk for tubular toxicity when rilpivirine is given in combination with tenofovir.

Uncertainty in the knowledge about the unfavourable effects

An extensive list of NNRTI-associated mutations (n= 39) constituted exclusion criteria in both phase 2b and phase 3 (around 10% of all screening failures). Many of these NNRTI-associated mutations were quite infrequent though, and were neither seen in the in vitro resistance profile of RPV, nor in patients failing RPV therapy in the trials. In the final analyses of all data a list of 15 RPV-associated mutations is

proposed to constitute those baseline mutations precluding RPV therapy in treatment naïve patients. This list covers the majority of the population not included in the trials, and the analyses behind it are endorsed. The combined frequency of these 15 mutations is high enough in untreated patients to request that resistance testing should be done prior to the use of RPV. This is reflected in the indication: as with other antiretroviral medicinal products, genotypic resistance testing should guide the use of rilpivirine and cross reference is made to the relevant sections 4.4 and 5.1 of the SmPC.

To perform resistance testing prior to the use of RPV is in line with the general recommendation in Europe - which implies that a baseline resistance testing should be done prior to starting HIV therapy (Vandamme et al, 2011). The other mutations used as exclusion criteria, not included in this list, were deselected by the company after final analyses of pre-clinical and clinical data; they were not found to affect activity in vitro and were not seen in any significant numbers in those failing RPV. Although they were formally not properly studied in vivo, the impact in response rates of the phase 3 studies would not have been significantly affected by their presence in the list of exclusion criteria. Future follow-up of resistance should be provided according to the proposed pharmacovigilance measures and the correctness of associated mutations should be confirmed.

In a thorough QT-study a somewhat unexpected QTc increase above the threshold (just above 10 ms for female subjects) was seen at doses 75 mg or higher. As consequence any risk factor for QT prolongation was an exclusion criterion in the phase III trials giving an uncertainty about the safety of RPV in individuals with such risk factors. However, no difference in QTc increase was seen for the 75 mg dose compared to and efavirenz in the phase 2b study (using common 12-lead ECGs). Also no significant QTc change was noted in an interaction study with RPV 150 mg qd in combination with darunavir/r, which further doubles the exposure. Therefore, the clinical relevance of the QT-prolongation observed at a dose of 75 mg is currently unclear.

Furthermore, post-hoc analyses showed a low incidence for patients with risk of QTc prolongation at screening to phase 3, and observed risk factors were of limited clinical relevance. Therefore, as the 25 mg dose was not associated with QTc interval prolongation, no special warnings are required for the moment. A warning on QT prolongation with supratherapeutic dose (75 mg and higher) was included in section 4.4 of the SmPC.

The applicant could not provide additional safety data on parameters adequate for monitoring tubular injury (urine-protein, urine-β2-microglobulin etc), as these were not collected during the studies. However, other available data do not point toward tubular toxicity with rilpivirine. Still, given the fact that tenofovir exposure is highly dependent on renal clearance the effect of rilpivirine on renal clearance and creatinine levels is reflected in sections 4.2 and 4.8 of the SmPC, as well that rilpivirine was only studied in patients with normal renal function.

Benefit Risk Balance

Importance of favourable and unfavourable effects

As the targeted indication is the treatment of HIV-1 infection in ARV-naïve individuals, both tolerability and efficacy of the ARV regimen are of high importance; this is the start of a potential life-long treatment. In this light, the noted better tolerability of RPV compared to the golden standard EFV, is considered of clinical relevance. Also the qd dosage and low pill burden are advantages that can make it easier for patients to comply with therapy.

A prerequisite of the ARV regimen is its virological potency. Any inability to suppress HIV replication is considered of clinical concern as this may lead to resistance hampering 2nd line ARV treatment

options. Virological failure due to resistance should therefore be considered of greater clinical relevance than the tolerability of the regimen.

Benefit-risk balance

most relevant clinical endpoint (<50 copies/mL). The potential extra benefit over EFV relies in a better tolerability, all be it predominantly the first four weeks of treatment, and the patients convenience having one tablet, once daily as ARV regimen.

This benefit, together with the non-inferior efficacy, should be balanced against an overall 2-fold higher risk of RPV for developing virological failure and emerging resistance of which the latter has greater clinical consequences, as resistance to RPV was also more frequently associated with resistance development to the backbone NRTIs.

In the pivotal phase III studies, the overall risk of emergence of resistance appeared to be about 6% versus 3% for RPV and EFV, respectively. In further analyses it was shown that, the increased risk of emerging resistance with TCM278 is driven by patients with high baseline viral load (>100,000 copies/ml); these patients show lower virologic response rates and higher rates of virologic failure compared to EFV. On the other hand, for patients with baseline viral load ≤100,000 copies/ml TCM278 showed numerically higher response rate and a low risk of emerging resistance and in the same order of magnitude as observed for EFV. It can be expected that the ongoing studies up to 96 weeks will confirm the observed comparative efficacy and safety profiles of RPV.

Based on these arguments the limited benefit of better tolerability does not weigh against the higher risk for emerging resistance for treatment naïve patients at large - the risk of failure and its consequences are not acceptable for patients with a high baseline viral load, taking into account the performance of other available first line options for such patients. Therefore, the CHMP considers that the benefits outweighs the risks when RPV is restricted to patients with low baseline viral load.

Since the 25 mg dose is at the edge of being suboptimal, it is crucial that the exposure is not lowered (concomitant drugs, need for intake in fed state); there is always a risk that these issues are handled less strict in clinical practice than within a clinical trial, where everything is closely monitored. This risk was emphasized in the respective sections of the SmPC. Therapy should be guided by resistance testing as it is considered current good clinical practice in line with the general recommendation according to updated European treatment guidelines.

In clinical practice rilpivirine might be considered a potential option for switch once viral load has been broken with more potent drugs. Although the drug might be an effective option, there is currently no data available in support of such use. The applicant will monitor such use in clinical practice and new studies are on going on use in patients switching from other therapies to RPV.

Discussion on the Benefit Risk Balance

From an individual patient perspective, the reason for judging an ARV agent to be abandoned from the 1st line regimen, either intolerability or insufficient virological effect, is not so relevant as long as alternate future, 2nd line, options are still available. Rilpivirine presents a higher risk for emerging resistance limiting 2nd line options, although nevertheless available 2nd line options in general still remain. However, whenever possible, avoidance of emerging resistance is considered more critical than tolerability.

The restriction of the indication to patients with low baseline viral load resolves the major concern on increased risk of emerging resistance compared to efavirenz. As mention above although the potential consequences of developing resistance are of greater concern with RPV given the potential loss of

treatment options, the absolute risk is low and available 2nd line options still remain. Interaction with drugs that lower RPV exposure is contraindicated given the potential lower efficacy and subsequent emergence of resistance and RPV must be taken in fed state. Within these restrictions, in patients with low viral load the risks are outweighed by the benefits of RPV showing a comparable high virologic response rate with a better tolerability profile to efavirenz and a favourable once-daily dosing regimen.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Eviplera "indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. The demonstration of the benefit of the combination emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate in antiretroviral therapy is based on week 48 safety and efficacy analyses from two randomised, double-blind, controlled Phase III studies in treatment-naïve patients (see section 5.1). As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of Eviplera (see sections 4.4 and 5.1)." is favourable and therefore recommends the granting of the marketing authorisation.

1.8. Fampyra

Benefits

- Beneficial effects

In the clinical studies MS-F202/203/204, a statistically significant difference in responders was observed. The results of the three studies were similar, overall the responder rate was 8.9% for the placebo group versus 37.2% for the fampridine group (difference 28.4%, CI95% 22.1%; 34.2%). The responder definition was based on the walking speed assessed in the Timed 25 feet walking test (T25FW), i.e. the time in seconds it takes to walk 25 feet. A responder was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period as compared to the maximum speed for any of the off-treatment visits. Overall efficacy in terms of responders appeared homogenous across subgroups identified. Also the difference in proportion of subjects with a 20% improvement in walking speed i.e. 13% versus 31% for placebo and fampridine was statistically significant.

In the main studies MS-F203/204, the differences in mean changes from baseline in walking questionnaire, muscle strength and spasticity were either statistically significant or showed a trend in favour of fampridine.

The pharmacokinetics of fampridine is linear; fampridine is absorbed in a dose proportional manner and there is no accumulation after repeated doses. Moreover, it is unbound to plasma proteins and almost completely eliminated via urinary excretion. The major fraction recovered was contributed to the parent drug.

- Uncertainty in the knowledge about the beneficial effects

The main uncertainties concern the value of the Timed 25 Foot Walk test and value of the responder definition derived from it, as no experience exists in the evaluation of treatments for symptomatic

treatment in multiple sclerosis so far. Further, the clinical meaningfulness of the observed statistically significant differences has not been established.

The Timed 25 feet walking test (T25FW) in essence measures the speed of walking. The T25FW is considered more a pharmacodynamic endpoint rather than a clinically relevant outcome. The submitted studies have demonstrated the proof of concept, i.e. that fampridine has a small, but statistically significant effect on the speed of walking over a short distance. The significance across broader aspects of walking has not been shown, which makes the test unacceptable as a clinically relevant outcome measure. The use of walking speed as a surrogate of walking ability is uncertain.

The clinical relevance of the effect observed is highly uncertain. Any improvement in the speed of walking over a short distance is hard to interpret in terms of clinical relevance. As stated above more important is whether speed can be maintained for a while, increasing the range of action. For the secondary endpoints, the mean changes from baseline in MSWS-12, LEMMT and Ashworth scores within the study groups were small, let alone the differences in change from baseline between the study groups, although statistical significance or a trend to statistical significance was observed. For the Subject Global Impression and Clinician Global Impression there is no or almost no shift in median indicating that the improvement might not be perceived as substantial. The majority of subjects perceived no satisfaction or improvement let alone a substantial improvement. This confirms the picture that emerges from the scatter plots presented by the applicant at the oral hearing. The change in walking speed versus the MSWS-12 score, CGI and SGI categories showed a large overlap. Visually there was no separation between the placebo and fampridine study arm.

In agreement with this, the Scientific Advisory Group (SAG) concluded that a significant effect across the broader aspects of walking has not been shown, which makes the test unacceptable as a clinically relevant outcome measure. Walking speed does not provide information with regard to the quality of walking. There are several different aspects of walking that can be affected by MS, including coordination, balance and stamina. Outcome measures that address these aspects specifically have not been presented. It was noted that patients consider endurance as more important than the speed to bridge a short distance, as this determines the range of action.

Based on the literature submitted the range of walking speeds observed in the fampridine studies does not affect the range of action.

The applicant has argued that a 20% improvement in walking speed, as measured by the T25FW, results in clinically relevant changes in the clinical outcome. This was questioned by the CHMP, as the difference in proportion of a 20% responder, i.e. 13% (placebo) versus 31% (fampridine) did neither shift the overall mean scores in MSWS-12 nor the median scores of SGI and CGI. Regarding the MSWS-12, the validation of the 6 point change in the MSWS-12 as defined was questioned as the data were limited (based on a poster) and not based on independent studies. Importantly, the percentage of patients being satisfied by treatment was equal for subjects on placebo and fampridine i.e. 35% in study MS-F203 and 26% in study MS-F204. If the difference in proportion of 20% responder, i.e. 13% (placebo) versus 31% (fampridine) was considered clinically significant, it would be expected that these figures would be different. Regarding the CGI, in study MS-F204 but not in study MS-F203, the proportion of patients with a shift in CGI category separated from placebo. However, this was inconsistent with the SGI that the clinician perceives an improvement that is not perceived at all as an improvement by the patient (SGI).

The applicant suggested identifying responders and continuing treatment only in responders and proposed a treatment algorithm in the SmPC. However, no conclusion could be drawn with respect to the clinical relevance of the 20% improvement in walking speed as stated above. Although responder definitions are inherently arbitrary, it has not been shown that improvement in responders, either

defined according to the responder definition in the clinical trials or defined as 20% improvement, is of general benefit for this group of MS patients. Hence, the suggestion by the applicant to resolve the issue in the SmPC was not considered acceptable.

Supportive evidence for efficacy was scarce, e.g. PD studies (electrophysiological studies), a dose-response relationship, a plasma-concentration relationship, efficacy on sign/symptoms of other demyelinated areas, was not observed. Further, the effect of fampridine was similar despite large differences in duration of disease, EDSS stage or MS-type.

Maintenance of effect remains unclear. The observed decline in effect may be attributed to disease progression or lack of effect or both. This has not been evaluated appropriately by the applicant.

Hence, it remains uncertain to which extent improvement in walking speed, and particularly the walking speed as observed in the studies, is indeed a benefit for the patient with respect to walking ability, walking quality, endurance and increase in range of action.

Risks

- Unfavourable effects

Fampridine is a selective potassium channel blocker, which acts on subtypes of K channels expressed in excitable cells such as neurons, cardiac and skeletal muscle, smooth muscle and lymphocytes. Hence, effects of fampridine in these tissues could be expected and this has been addressed correspondingly in the safety questions posed to the applicant. Given this mechanism of action and the PK data so far, fampridine should be considered as a narrow therapeutic index drug, unless proven otherwise.

In the PK-PD models AEs and CNS-AEs were related to higher C_{max} and AUC of fampridine. This was confirmed in the clinical studies, i.e. an increased frequency of AEs was observed in the patients with abnormal renal function as compared to normal renal function. Hence, the safe use in patients with mild renal impairment was questioned by the CHMP. This highlights drawback of having just one dose strength of 10 mg, which limits dosing flexibility and poses problems in patients with renal impairment including the elderly. The MAH could not justify a safe dose in the elderly.

Identified risks concern possible coordination abnormalities, anxiety, depressive mood, insomnia and an increased risk for infections.

A prominent signal is the higher incidence of dizziness, pain of various types, paraesthesia, balance, coordination disorders and falls, which all indicate a possible over-stimulation of the afferent nerve tracts, i.e. an abnormal sensory feedback affecting motor coordination. Related to this is the excess of MS symptoms and MS relapses in the fampridine group which might include misclassifications of symptoms of over-stimulation of the sensory fibres. Although most of these events were apparently transient, as patients may get used to them, in a substantial proportion of patients these events persisted. Moreover, considering the efficacy, it was questioned whether the excess in events, even if transient, i.e. persisting 0-8 weeks, is acceptable.

A higher incidence of anxiety, depressive mood and insomnia was observed in the fampridine treated patients. While for the depressive events (and also the suicide events) it is rather difficult to judge if these were related to the fampridine treatment or to the MS itself, the signals of increased anxiety and insomnia were easier to distinguish. For a drug which would be applied chronically, this might present a serious problem in the long run.

Further an increased frequency of UTI, respiratory tract infections and constipation was observed in the fampridine arm. This raises the question whether fampridine does affect the motility of the

urogenital, respiratory and gastrointestinal tract. Since there are some changes in the blood counts indicative for suppression of haematopoiesis, a compromised immune response may form an alternative explanation for the differences in infection rates.

- Uncertainty in the knowledge about the unfavourable effects

Pharmacodynamic interaction of fampridine with anti-epileptic and anti-arrhythmic agents is expected, based on the mechanism of action of fampridine. This was not investigated sufficiently and therefore remained a point of concern.

Cardiovascularly compromised patients were excluded from the trials. Given the mechanism of action, the safety in cardiovascularly compromised patients remains to be established. As a matter of fact, even in the absence of these patients in the MS population studied, these events have already been observed with higher incidence in the fampridine group than in the placebo group. Hence, the true magnitude of the cardiovascular risk could not be estimated from the short term safety data, and long term data so far are insufficient. The benefit/risk in this population is therefore uncertain.

Another uncertainty is related to the benefit/risk in the elderly multiple sclerosis patients, since very few elderly patients were included in the studies. Adverse events may be a specific issue in the elderly, as the product is eliminated renally, but also because this population might be more sensitive to CNS effects.

Long term safety data are insufficient for a conclusive assessment of long term safety. 35% drop-out rates suggest that the benefit/risk balance changes over time.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

A statistically significant effect in terms of a consistent improvement in walking speed in the short-term studies is considered established. However, the value of the T25FW and the responder definition derived from it is questioned. The clinical relevance of the statistically significant differences is highly uncertain. The applicant was not able to relate the observed changes in walking speed to clinical meaningfulness. In particular, neither patients nor physicians perceived the change in walking speed as an improvement, whereas overstimulation may impair walking quality and the range of action. Supportive evidence of efficacy is limited and whether the decline in effect under long term treatment is due to disease progression or lack of effect or both remained unclear. Hence, maintenance of efficacy is unclear.

Identified risks include coordination abnormalities, but also anxiety, pain, insomnia and an increased risk of infections. There are uncertainties concerning the long term safety, safe use in the elderly, cardiovascularly compromised patients, patients at risk of seizures including epileptic patients and patients with mild renal impairment.

- Benefit-risk balance

The benefit / risk of fampridine is considered unfavourable.

Discussion on the benefit-risk balance

Concerning the quality and non-clinical data, no major objections remained at the end of the review.

However, regarding the clinical data too many uncertainties concerning both benefit and risk, preclude a recommendation for a positive opinion.

Basically, these refer to the need to substantiate the clinical relevance of the effect observed on walking speed. With respect to safety, the observed abnormal coordination may counterbalance a positive effect on the walking speed. Long term efficacy and safety remains unclear. In addition, relevant issues related to the mechanism of action of fampridine need further attention for a positive recommendation, i.e. the safety in cardiovascularly compromised patients, patients at risk of seizures including epileptic patients, the elderly and patients with mild renal impairment.

The proposal of the applicant to resolve these problems in the SmPC was not considered acceptable by the CHMP. The lack of relationship between the walking test and clinical benefit precludes a recommendation of accepting this symptomatic treatment. The efficacy on a clinical outcome remains questionable, long-term efficacy declines and long-term safety data are insufficient, precluding accepting a risk of overstimulation affecting walking ability.

One member of the CHMP expressed a divergent position to the outcome of the benefit-risk assessment and considered the benefit-risk balance of fampridine for improvement of walking ability favourable. In particular, this member was of the view that results of fampridine in the pivotal trials were consistent with a clear symptomatic effect that might be of importance in a subgroup of multiple sclerosis patients, for whom there are no alternatives besides physiotherapy. With respect to the safety profile of the product, namely the risk of seizures, the member considered that these are manageable as their frequency is low and specialised prescribers will supervise use of the product.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the benefit-risk balance of fampridine in the treatment of adult patients with multiple sclerosis for the improvement of walking ability was unfavourable and therefore did not recommend the granting of the marketing authorisation.

The CHMP considered that:

- The statistically significant but small improvements in walking speed could not be related to meaningful improvements in walking ability e.g. walking quality, endurance and increased range of action. Furthermore, the improvement in walking speed was not accompanied by a clear and consistent overall benefit, as assessed by doctors and patients.
- The small uncertain benefit does not outweigh the increased incidence of adverse events e.g. anxiety, insomnia, seizures, infections and events indicating an abnormal sensory feedback/overstimulation that may negatively affect walking ability.
- The long-term efficacy as well as long-term safety have been insufficiently established.
- The benefit/risk in relevant subpopulations, such as the elderly, cardiovascularly compromised patients and epileptic patients is unclear.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Overall conclusion on grounds for re-examination

The CHMP assessed the detailed grounds for re-examination and argumentation presented by the applicant in writing and in the oral explanation and considered the views of the re-examination Scientific Advisory Group Neurology.

The latest modified indication applied for by the applicant was

"Fampyra is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)."

With the re-examination, the CHMP considered whether the application for Fampyra would meet the requirements for a conditional marketing authorisation, taking into account the public health interest and the fact that Fampyra is a medicinal product which aims at the treatment of a seriously debilitating disease.

The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/Ec, is positive.

At the end of the re-examination procedure the CHMP concluded on a favourable benefit-risk balance of Fampyra. The CHMP considered that approximately one third of patients may benefit from the treatment. The CHMP recognised that the product demonstrated benefits in terms of improving walking speed together with improvement on MSWS-12 (multiple-sclerosis walking scale score), i.e. a patient reported outcome measure. Using these two efficacy outcome measures, for which a certain level of relationship was observed, the CHMP considered that it was possible to define a patient population benefiting from treatment with fampridine on both scales. As described above (CHMP position on ground for refusal No. 1), new elements were brought in by the re-examination SAG Neurology; in particular, the 20% improvement based on walking speed was suggested to be of potential relevance, if correlated to patient-reported outcome measures. Furthermore, practical approach to evaluating response to treatment on an individual level, based on monitoring of response by means of a walking test as suggested by the SAG Neurology, was accepted by the CHMP during the re-examination procedure.

Nevertheless, the CHMP was of the opinion that the understanding of benefit provided by fampridine is not completely explained by the data currently available; in particular, other important aspects of walking such as balance, endurance and walking distance that constitute additional evidence of improvement in the overall walking ability were regarded relevant. The CHMP considered that further data obtained in a controlled setting of a clinical trial are needed and that the validity of the currently proposed criteria for identification of responders should be further evaluated. Therefore, the CHMP requested that the marketing authorisation should be granted subject to a following condition:

"To conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment. The study report is to be submitted by 30 June 2016."

The CHMP considered that the safety profile of fampridine is dominated by adverse events related to the expression of CNS overstimulation, which is concordant with fampridine´s mechanism of action and that these adverse events are dose-dependent. The CHMP noted that although the adverse events were more frequent in the treated group in the clinical trials, they rarely led to discontinuation and were rated as mild and transitory. The CHMP considered that the main safety issue among events related to overstimulation were seizures, because of the level of seriousness as a health event.

The data presented by the applicant did not allow for quantifying the true incidence of seizures associated with fampridine, but the added risk level was considered low and dose-dependent (some of the events observed were related to medication errors associated with overdose). In their meeting, the re-examination SAG Neurology discussed the seizure risk and recognized that seizures occur rarely in patients treated with fampridine, further data presented by the applicant suggesting that occurrence of seizures is not a major concern for the overall benefit-risk balance of the product. The SAG Neurology

recommended that pre-existing seizure disorder should be a contraindication to treatment with fampridine. The CHMP took the SAG Neurology recommendation into account and furthermore, also considered that literature[9] and the applicant´s data from clinical studies with other multiple sclerosis products (disease-modifying drugs) providing evidence on the background incidence of seizures in MS patients were re-assuring in terms of fampridine´s low level of the added risk.

The CHMP concluded that the current therapeutic dose is border-line and that any increase (e.g. overdose) might put patients at higher risk of seizures. In this context, the CHMP considered that an observational study further quantifying the risk of seizure will be conducted, as described in the Risk Management Plan.

Unmet medical needs will be fulfilled

The CHMP considered that the benefits of Fampyra were observed in the field of symptomatic treatment of multiple sclerosis, where there is no other drug approved. In this context, Fampyra was considered to address an unmet medical need by providing symptomatic treatment for walking impairment in patients with MS.

The CHMP further considered that given the lack of symptomatic treatment in MS, extemporaneous formulations of 4-aminopyridine are in use, which might be of lower quality standards and also pose safety problems linked to limited control over their dosing. The formulation of Fampyra, i.e. prolonged-release tablets, was considered to tackle these problems. Thus, the CHMP concluded that placing Fampyra on the market would help address the unmet medical need.

The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The CHMP considered that overall, approximately one third of patients treated might get a relevant benefit from the treatment and, in the context of the unmet medical need described above, concluded on a benefit of the immediate availability of Fampyra on the market. The CHMP also considered that patients benefiting form the treatment can be identified on the basis of their response at an early stage and that treatment can be discontinued in patients not benefiting, hence preventing unnecessary exposure. The CHMP was of the opinion that data currently not available and required additionally, i.e from *a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment* do not preclude concluding on a positive benefit-risk balance for the target population.

At the time of the CHMP opinion, there was a quality issue that will be resolved as Follow-up Measure within an agreed timeframe. This issue relates to confirming the in-use period to product close to the end of the shelf-life. However, this issue was not expected to have a negative impact on the benefit-risk balance of the product.

In conclusion, the CHMP confirmed that the criteria needed for granting a Conditional Marketing Authorisation have been met.

Recommendation following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Fampyra in the following indication:

[9] Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. Mult Scler 2002; 8 (6):495-9

"Fampyra is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7)."

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.

1.9. Gilenya

Benefits

- Beneficial effects

Fingolimod is a structural analogue to endogenous sphingosine, phosphorylated to the active moiety FTY720-P which down-modulates S1P1 receptors on lymphocytes and slows down the S1P-S1P1-dependent egress kinetics of CD4 and CD8 T cells and B cells from lymph nodes. This reduces the recirculation of lymphocytes from lymph nodes into blood and CNS. In vivo effects were demonstrated in several EAE disease models.

Multiple sclerosis is a chronic, inflammatory, demyelinating disease of the central nervous system and is the one of the most common causes of neurological disability in young adults. In humans, fingolimod leads to a dose-dependent decrease in peripheral blood lymphocyte count. This may potentially reduce the infiltration of pathogenic lymphocyte cells into the CNS where they would be involved in inflammation and nervous tissue damage.

Currently, no oral medication is approved for the treatment of relapsing multiple sclerosis. All available disease modifying therapies for multiple sclerosis are administered subcutaneously, intramuscularly or intravenously. The drug product has the advantage that it can be administered orally without regard to food intake. The proposed dose is 0.5 mg daily.

Study D2301 was a 2 year, double-blind, placebo controlled randomized study in patients 17 to 55 years, with RRMS and an EDSS score of 0 to 5.5 who had had at least one relapse in the previous year or at least two relapses in the previous two years. Overall, this pivotal phase III study of adequate duration and methodology, showed consistent and robust efficacy of fingolimod (1.25 and 0.5 mg) both on the primary efficacy criteria (aggregate annualized relapse rate ARR) and all secondary clinical and MRIs efficacy criteria as compared to placebo. The results on primary efficacy parameter (ITT population) showed statistically significantly lower aggregate ARR at all doses tested (0.5 mg : 0.18, 95% CI: 0.15, 0.22; 1.25 mg: 0.16, 95% CI: 0.13, 0.19) versus placebo (0.40, 95% CI: 0.34, 0.47),representing relative reduction of 54% and 60%, respectively in the annualized relapse rate (ARR ratio: 0.40 and 0.46 for 1.25 mg and 0.5 mg, respectively). Results on the key secondary endpoint, time to disability progression confirmed at 3 months, was also statistically longer with all doses tested than with placebo. Fingolimod reduced the risk of disability progression, confirmed at 3 months, over the 24-month study period (0.5 mg: HR= 0.68, 95% CI: 0.50, 0.93, p=0.017; 1.25 mg: 0.5 mg: HR= 0.70, 95% CI: 0.52, 0.96, p=0.024) as compared to placebo. Both doses showed consistent efficacy on primary and key secondary endpoints. The results did not seem to evidence clinical difference of relevance in the efficacy results for the two doses, and the choice of 0.5 mg dose choice was considered appropriate.

Study D2302 was a one year duration, phase III, double-blind, double dummy, 2 doses of fingolimod (1.5 mg and 0.5mg, once a day) active controlled randomized study of one year duration, in patients 18 to 55 years with RRMS and an EDSS score 0 to 5.5 who had had at least one relapse in the previous year or at least two relapses in the previous two years. Overall, this well design active controlled study

showed superior efficacy of both doses (1.5 mg and 0.5 mg) of fingolimod as compared to Avonex on primary efficacy criteria (ARR). For the ITT population the aggregate ARR was statistically significantly lower with fingolimod at all doses tested (0.5 mg : 0.16, 95% CI: , 0.122, 0.212, p<0.001 ; 1.25 mg: 0.20, 95% CI: 0.157,0.264, p<0.001) versus interferon beta-1a (0.33, 95% CI: 0.262, 0.417), representing relative reductions of 52% and 38%, respectively, in the annualized relapse rate (ARR ratio: 0.62 and 0.48 for 1.25 mg and 0.5 mg, respectively). Regarding key secondary endpoints, both fingolimod treatment groups had a lower mean number of new or newly enlarged T2 lesions compared to the interferon beta-1a i.m. group, which reached statistical significance for both the fingolimod 1.25 mg group (p<0.001) and the fingolimod 0.5 mg group (p=0.004).

There was no obvious evidence of rebound effect based on MRI data.

Additional post-hoc subgroup analyses in highly active patients with RRMS were performed by the applicant to evaluate the benefit-risk in a restricted population. Results of these subgroups analyses were consistent with those obtained in the overall population.

- Uncertainty in the knowledge about the beneficial effects.

Regarding key secondary endpoints, there was no difference between the two fingolimod treatment groups and the interferon beta-1a i.m. group in the time to 3-month confirmed disability progression as based on Kaplan-Meier estimates (0.5 mg: difference=2.03, 95% CI: -1.42, 5.47, p=0.247, 1.25 mg: difference=1.30, 95% CI: -2.26, 4.86, p=0.498) . This may be explained by the shorter duration of the trial D2302 (one year) and low active population included. However, efficacy on the 2 year placebo controlled study (D2301) is supportive on this aspect.

Relapsing MS including both RRMS and SPMS that still experienced relapses was not studied.

The elderly population was not studied.

There is a lack of information concerning disease activity (frequency and severity of relapses) after discontinuation of fingolimod.

Risks

- Unfavourable effects

Safety concerns associated with the biologic effects of fingolimod were reported on the cardiac, ocular, immune, hepatic, and pulmonary systems. These were also observed in the non clinical studies.

Infection is an important identified unfavourable effect. The incidence of infection and infestation serious adverse events appeared to be increased during the 24 month-treatment. A total of 3 cases of disseminated herpes infection were reported in patients treated with fingolimod 1.25 mg. In these cases, 2 deaths were reported. The third patient had disseminated herpes zoster with pulmonary involvement and made a complete recovery after treatment with aciclovir therapy.

Among the cases for malignancies reported in the fingolimod groups , a total of 3 cases of lymphoma in MS clinical development program were identified and a causal relationship between those cases and treatment by fingolimod can not be excluded. With a population more than 4,000 patients exposed to fingolimod (approximately 10,000 patient-years, the estimated incidence of lymphoma with fingolimod is 3 in 10,000 patient years (95%CI: 0.6-8.8 per 10,000 patient years). In contrast, no lymphoma has been reported in the placebo arm nor in the interferon arm.

Other unfavourable effects that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients included: reductions in white blood cell counts (lymphocytes and total WBC), bradycardia on treatment initiation (Day 1), elevations of liver enzymes (in particular increases

in ALT and GGT), macular edema, hypertension and dyspnea. In addition, a number of cases of severe neurological adverse events were reported including 2 cases of PRES (Posterior reversible Encephalopathy Syndrome) and one fatal case suggestive of acute disseminated encephalomyelitis (ADEM).

In preclinical studies, fingolimod has shown a teratogenic potential. A total of 30 out of 52 pregnancies were reported in fingolimod-treated patients in the clinical studies including a total of 2380 female patients as of 29 January 2010. Thirteen successful deliveries with 12 normal newborns and 1 case report of congenital shortening of the right leg with congenital posteromedial bowing of the tibia were observed. Limited information was available on abortions, however, one abortion was reported to be due to Fallot's tetralogy (fetal abnormality) in a female patient on fingolimod 1.25 mg. Considering the the population fingolimod is intended to be used for, this finding is considered as an important unfavourable effect.

- Uncertainty in the knowledge about the unfavourable effects.

Considering the heterogeneous safety profile, further long term data are required and a post-approval 5 year safety study will be conducted as part of the risk management plan to further investigate a number of risks and potential complications such as hypertension, liver enzyme elevation, macular edema, infections, thromboembolic events, skin cancer and other malignant neoplasms.

Additional data are required to further document the potential risk of malignancies and this will be additionally monitor in a long term observational study which is part of the risk management plan.

PRES syndromes and other neurological atypical manifestations (ADEM) were reported, the relationship with fingolimod cannot be excluded and this concern has been identified as an important potential risk.

Given the effect of teratogenicity seen in rats and the embryo/fetotoxic effect in rabbits, an effective contraception is recommended during treatment and 2 months after treatment discontinuation. A pregnancy exposure registry to prospectively collect outcome data on the babies born to women treated with fingolimod is an additional pharmacovigilance activity set up as part of the risk management plan.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The effects demonstrated versus placebo as well as the active comparator Avonex were considered clinically relevant in the overall population. Oral administration was considered to be of particular benefit given that the currently available therapies are using the parenteral route. A number of important safety concerns have been identified related to the mechanism of action that is first in the class. The safety of fingolimod is characterised by a heterogeneous profile which required to recommend a restricted use in multiple sclerosis population as well as a number of measures to ensure safe and effective use of the product. Consistent treatment effects wer observed in highly active group of RRMS patients as compared to the overall population and therefore this restricted population was recommended for the indication.

- Benefit-risk balance

Having considered the benefits of this first oral treatment for multiple sclerosis over the potential and identified risks, the CHMP concluded that the benefit risk balance for Gilenya is positive for the following indication:

"GILENYA is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

Patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.

A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,

or

patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI."

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Gilenya as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.
A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

was favourable and therefore recommended the granting of the marketing authorisation.

1.10. Halaven

Benefits

- Beneficial effects

In advanced stages of breast cancer the most important beneficial effects are increased overall survival (OS) in combination with a good tolerability of the drug, since this may impact the quality of the remaining time in life. Another important beneficial effect is prolonged progression-free survival (PFS), as time without tumour progression (and accompanying symptoms and psychological effects) are also of significant value for the quality of the remaining life.

The updated OS analysis showed consistent results with the original analysis, including HR 0.805 (95% CI 0.67, 0.96), p-value (0.014) and an increase of median OS from 75 to 82 days (2.7 months). In the Investigator assessment-based analysis of PFS the HR was 0.76 (95% CI 0.64, 0.90).

Since eribulin is a tubulin-targeting drug, the issue of cross-resistance between eribulin and other tubulin-active drugs was investigated. The positive effect on OS and PFS was seen in both taxane-refractory and non-refractory groups of patients. In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI 0.56, 0.96) for patients not taxane-refractory. In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.

A second subgroup of interest was the capecitabine-naïve patients. The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

There were no important differences in terms of clinical efficacy with regard to HR point estimates and CIs for any of the sub-group analyses conducted.

Risks

- Unfavourable effects

Eribulin is eliminated mainly by biliary excretion and the transporter involved in unknown. If the biliary excretion is completely inhibited, this could result in a 250% increase in systemic exposure. A general warning is included in the SmPC but there may be inhibitors marketed where the inhibitory effect on the transporter is unknown. Further clarifications concerning transporter inhibition, hepatic impairment and renal impairment will be addressed in future studies, which are part of the risk management plan.

There are clearly more AEs and treatment-related AEs overall associated with eribulin treatment compared with TPC, and the pattern is consistent with that of a tubulin acting cytotoxic agent. With regard to the most frequent AE, asthenia/fatigue (occurring in >50% of patients), the difference was mainly due to grade 1-2 AEs, however. Most (3/4) cases of the other tubulin-inhibiting typical AE, peripheral neuropathy (occurring in around 35% of patients), were also grade 1-2. Even so, it was the AE most frequently causing treatment discontinuation, and the cumulative peripheral neuropathy is a factor likely to affect the quality of life during an extended time, possibly for the remainder of many patients' lives. The median Time to onset of peripheral neuropathy was 23 weeks in both pooled safety populations (AETP and BCP), and median Time to grade ≥ 2 peripheral neuropathy was 43 and 54 weeks, respectively. Time to resolution of peripheral neuropathy is not possible to assess with any degree of certainty, due to a large proportion of definitely censored patients, the most conservative estimation currently being 13 weeks, based on less than 20% being resolved. In the 32.5% of the BCP patients who experienced peripheral neuropathy events of CTC grade *higher than baseline* neuropathy, the event was resolved in 42% of cases, in the sense returning to baseline or lower. Twelve of 37 (32%) patients who discontinued treatment due to peripheral neuropathy resolved, as did 31/40 (77.5%) of patients who had their dose delayed or reduced due to peripheral neuropathy, indicating that peripheral neuropathy to some degree can be managed.

The incidences of neutropenia grade 3-4 and febrile neutropenia were high (45% and 4%, respectively), despite that one fifth of patients received G-CSF. A shift in absolute neutrophil count from grade 0 to 4 in cycle 1 was seen in 15.5% of patients. Neutropenia did not cause treatment discontinuation in high frequency however, and the impact on quality of life from a hospitalization due to such an event is normally of short duration. The long-term impact on bone marrow function and resulting increased risk of neutropenia is a problem shared with many classes of cytotoxic agents.

The incidence of nausea and vomiting is similar to that of other drugs used in this indication, as shown by the TPC-arm of Study 305, and may be controlled by anti-emetic premedication.

The incidence of thromboembolic SAEs (pulmonary embolism and deep vein thrombosis) is around what may be expected in this disease and therapy setting. The TEAEs with an outcome of death unrelated to disease progression was low (<1%), and a majority of these AEs were infections, as can be expected of immunosuppressive agents like eribulin.

In the BCP 12% of the patients received anti-emetics as treatment for adverse reactions during cycle 1, and 46% received anti-emetic prophylaxis, which in 1/2 of the cases included the corticosteroid dexamethasone. The incidence of nausea/vomiting in the subgroup of patients who did not use antiemetic during cycle 1 (42% of all patients) is consistently lower compared with the subgroups who used anti-emetics, most likely reflecting an enrichment in the anti-emetic treated groups of patients with current or previous nausea/vomiting reactions and consequent increased risk of these AEs. Thus, the treating physicians appear to have successfully identified a patient population at risk of nausea and vomiting, and the "natural" incidence of these adverse events is likely to have been even higher if left without anti-emetic prophylaxis. It does appear, however, that the prescribers can handle this situation wisely. The frequencies reported in the BCP of 36% treatment-related nausea, and 14% treatment-related vomiting would motivate antiemetic premedication with one dose of corticosteroids, according to international recommendations. While corticosteroid anti-emetic prophylaxis may not be required for all patients, it should be considered.

There is a difference in the frequency of psychiatric disorders, 12 % in the TPC arm vs. 19% in the eribulin arm, and 22% in the pooled eribulin populations. The difference appears mainly to be driven by the preferred terms depression at 5 vs. 1% (additionally supported by depressed mood, mood altered, and mood swings) and insomnia at 8 vs. 4%. Some explanations for these differences have been given by the Applicant, including corresponding differences in the patients' histories of psychiatric disorders (17% vs. 14%, in the eribulin and TPC arms, respectively), and in baseline symptoms of depression (7.7% vs. 4.7%) and insomnia (8.9% vs. 6.7%). The overall frequency of baseline psychiatric disorders was 38.6% in the BCP population, and in Study 305 it was 33.0% in the eribulin arm and 28.3% in the TPC arm. The Applicant has also shown that the risk of experiencing psychiatric AEs is higher in patients with a history of psychiatric disorders.

- Uncertainty in the knowledge about the unfavourable effects

The pharmacokinetics of eribulin is presently not fully characterised. The main pathway of elimination is biliary excretion and at present there is no information on which transporter(s) is involved in the process making predictions of drug-interactions resulting in increased eribulin exposure impossible to perform. If the biliary secretion is completely inhibited, the exposure (AUC) could increase by 250%. CYP3A4 is an important drug metabolising enzyme. *In vitro* data indicate that eribulin may inhibit CYP3A4 in the liver. No *in vivo* data is available. If eribulin inhibits the enzyme significantly *in vivo*, this may lead to interactions with a number of drugs. The potential for drug-drug interactions is adequately reflected in the SmPC. Drug-drug interaction studies are being conducted (see 2.7 Risk Management Plan)

The potential risk for cardiac arrhythmias has not been adequately evaluated. Inhibition of IKr (hERG) *in vitro* was evaluated at a single concentration (30 µM). Therefore it is not possible to calculate an EC50 value for the estimation of safety margins. No QT prolongation was seen in conscious dogs but the highest tested dose (0.04 mg/kg) resulted in an exposure that was lower than the clinical. Furthermore, the dogs were given eribulin as a 60 min infusion, which probably made the difference in Cmax, i.e. the most relevant parameter to compare, larger still.

ECGs and QTc intervals were evaluated in the clinical Study 110. There were no signs of QT prolongation associated with the administration of eribulin, but as eribulin is a cytotoxic drug the study was not optimal to exclude such effects. Adequate information on QT prolongation is reflected in the SmPC (see section 4.4)

Time to resolution of peripheral neuropathy is not possible to assess with any degree of certainty, due to the high degree of censoring, > 80% of affected patients, only a few of whom still remained on therapy with ongoing neuropathy. While some information is available in the majority of patients who experienced peripheral neuropathy events of CTC grade higher than baseline (see previous section), the average Time to resolution and the proportion of the patients in whom the AE can be expected to resolve after discontinuation will not be known based on the present studies. There are however other ongoing studies that might shed more light on this issue, i.e. the randomised phase 3 Study 301 (E7389-G000-301), and the phase 2 Study 209 (E7389-G000-209), designed to specifically address the neuropathy safety issue (see section 7.7, Risk Management Plan).

Benefit-risk balance

- Importance of favourable and unfavourable effects

Considering that the comparator is chosen to be the most active and suitable for each individual patient, based on tumour characteristics and medical history, the magnitude of the OS results are considered clinically meaningful. Prolonged PFS is also of significant value to patients with incurable cancer and supports the survival findings.

Overall, the known toxicity and tolerability profile of eribulin is considered reasonably well characterised and in essence typical for cytotoxic drugs with this mechanism of action.

- Benefit-risk balance

In patients with advanced breast cancer, the benefits from eribulin in form of prolonged survival and progression-free survival are considered clinically relevant.

The incidence of neutropenia/febrile neutropenia was high and associated with cases of deaths. However, these are not considered to outweigh the benefits of treatment in terms of overall survival.

The nausea and vomiting reactions are seen with many cytotoxic compounds, and normally accepted when balanced against the beneficial effects. The frequencies in the present populations would suggest the use of corticosteroid anti-emetics according to internationally accepted guidelines. While corticosteroid anti-emetic prophylaxis may not be required for all patients, it should be considered.

Concerning peripheral neuropathy, this is an inherent problem with tubulin-targeting drugs, which can be acceptable in light of the benefits. The frequencies were not higher than for some other approved drugs, and the majority 3/4 of the events were grade 1-2. Robust data regarding Time-to-resolution of peripheral neuropathy will not be generated by the present studies, but other studies are ongoing, including one that specifically addresses this issue as primary objective (see section 2.7).

Remaining uncertainties concerning cardiac safety are part of the Risk Management Plan as an identified risk and addressed in PSURs.

In conclusion, the balance of benefits and risks is considered positive.

Discussion on the benefit-risk balance

In late-stage cancer the main safety issue is tolerability, while low-frequency SAEs are of less importance. The tolerability of eribulin is lower than that of some other agents used in latter lines of the disease, but this is accompanied by a relevantly improved chance of prolonged survival, which can be assumed to outweigh the tolerability-problems in the eyes of many patients and their prescribing doctors. Some of the identified and uncertain risks can be managed through the SmPC; further clarifications regarding the risks can be provided with further studies included in the RMP (see section 2.7).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Halaven monotherapy.

in the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

was favourable and therefore recommended the granting of the marketing authorisation.

1.11. Incivo

Benefits

The primary endpoint in the pivotal trials is sustained viral response (SVR), defined as undetectable virus 24 weeks after the end of therapy. This is virtually equivalent of cure of hepatitis C, as evidenced by data indicating that less than 1% of patients will relapse after this time-point. Achieving SVR effectively stops the progression of the liver injury caused by hepatitis C virus. SVR is a universally accepted endpoint in trials aiming at the cure of HCV infection.

Beneficial effects

In the pivotal -108 study in treatment naive patients, the SVR rate in the 12 week telaprevir arm was 74.7%, a 30.9% increase compared to the placebo+peginterferon alfa-2a+ribavirin arm. Shortened treatment duration compared to the present standard of care was possible for nearly 60% of treatment naive patients. The advantage of telaprevir was apparent across demographic and baseline disease categories.

In the pivotal -216 study in treatment experienced patients SVR rates in all three prior response subcategories were statistically significantly superior to placebo, with a total difference in SVR rates of + 47% with the addition of telaprevir to peginterferon alfa-2a and ribavirin. The advantage of adding telaprevir was also apparent regardless of viral subtype, baseline viral load or degree of liver injury. Also, in treatment naive and –experienced patients increased efficacy was evident across IL28B genotypes.

Available long term follow up data indicate the durability of SVR obtained with telaprevir. The addition of telaprevir to regimens with peginterferon alfa-2a and ribavirin represents a major advance in the treatment of the genotype 1, the quantitatively dominant HCV genotype.

Uncertainty in the knowledge about the beneficial effects

The optimal duration of therapy in treatment naive patients with cirrhosis is unclear. Also, the suggested treatment algorithm for relapsers is to some extent based on inference, though, taking the totality of data into account, the evidence is considered sufficient for its approval. Moreover, it is recognised that treatment durations might be further individualised, entailing the possibility of, e g., still shorter duration in very early responders. The efficacy of telaprevir in several important subgroups of patients, such as HIV co-infected patients and paediatric patients have not been studied. The possibility of using telaprevir in novel treatment regimens (e.g., regimens without peginterferon) in patients with decompensated liver disease is unclear, as there is considerable uncertainty about the appropriate dose to use. Clarifying the reasons for the low exposure to telaprevir found in non-HCV infected patients with moderate liver impairment (Child Pugh B) is of importance to clarify the potiential for use of telaprevir in this population. Finally, the impact on SVR of baseline resistant variants in telaprevir-naive patients, which can be detected by population sequencing, has not yet been fully clarified due to low frequency of such predominant baseline variants.

Risks

The main risks identified during the telaprevir development program include severe rash and serious cutaneous adverse reactions, and the selection of drug resistant variants in patients failing to reach SVR. Other risks include a moderate propensity to QT prolongation (supratherapeutic telaprevir exposure data are lacking). This may be a concern mainly when telaprevir is co-prescribed with other QT-prolongators, the most important in the target population being methadone.

Unfavourable effects

The major known risk associated with telaprevir therapy is severe rash, including serious cutaneous reactions. Approximately 5% of patients experience a grade 3 rash during treatment, and there were three at least possible cases of Stevens Johnson syndrome during the telaprevir development program. The frequency of severe cutaneous events (DRESS, Stephens Johnson Syndrome) is less than 0.5%.

Increased on treatment rates of anemia, lymphopenia and retinopathy were also seen. Also, in most cases treatment failure is associated with the selection of a telaprevir resistant viral population, likely cross resistant to other drugs in the class (though not to antivirals of other classes). Follow-up data indicate a gradual reversion back to the baseline population after treatment discontinuation in most patients. The consequences of the selection of resistance for future treatment attempts, however, remain unclear.

The applicant has instituted adequate virological stopping rules to prevent unnecessary exposure to failing telaprevir regimens. Also, the applicant has agreed to present data in the SmPC on the relation between lead-in response in the DS arm of the pivotal -216 study in the respective categories of prior non-responders, and the likelihood of SVR. Such data may in some cases be helpful for the clinician to make an informed decision on whether to treat with telaprevir or to wait for future treatment options, in patients that may have a relatively low likelihood of SVR even with the addition of telaprevir to peginterferon alfa-2a and ribavirin.

With some minor additions by the CHMP, the applicant has instituted appropriate warnings in the SmPC concerning the proclivity to QT-prolongation, including the risk of enhanced effects due to drug interactions.

Uncertainty in the knowledge about the unfavourable effects

While telaprevir related cutaneous adverse events and their management have been carefully characterised in the development program, there remains some uncertainty on how this will impact telaprevir treatment in a "real life" setting outside clinical trials. There was an excess reporting of retinopathy events during telaprevir treatment. It is unclear whether there is causality or if this is a chance finding. Importantly, as stated above, the consequences of selected resistant variants in patients failing therapy, as regards the efficacy of future therapies including NS3/4A inhibitors, are still not fully elucidated. As ribavirin is a teratogen, adequate anti-conceptive measures are necessary during therapy. Telaprevir causes a moderate decrease in ethinylestradiol and minor decrease in norethindrone exposure. It is unknown whether the magnitude of the decrease is sufficient to impair the efficacy of combination oral contraceptives and therefore appropriate warnings and recommendations have been included in the SmPC. Finally, it is unknown whether there are any human-specific metabolites not present in non-clinical toxicity studies.

Importance of favourable and unfavourable effects

Approximately 70% of HCV infections in the Western world are genotype 1. After about 20 years of infection, around 20–30% of patients with HCV will have progressed to cirrhosis, 5–10% will have end stage liver disease and 4–8% will have died of liver-related causes. In patients with cirrhosis, the 5-year risk of hepatic decompensation is approximately 15-20% and the risk of hepatocellular carcinoma 10%. HCV is the most common cause of liver transplantation in Europe. In this light, the public health gain with telaprevir therapy is likely considerable, and this benefit also applies to many of the individuals that will be cured by telaprevir. While the occurrence of severe cutaneous reactions is recognised and is an important concern in the management of patients treated with telaprevir, these were reversible and there were no fatal cases in the development program. As previously stated, the putative negative effects of selection of resistant variants is not full characterised, but may be more limited than thought prior to the emerging results of the telaprevir long-term follow up study.

Benefit-risk balance

Reaching SVR effectively ends the progression of HCV-related hepatic injury. In this light, the greatly increased SVR rates seen with telaprevir therapy must be weighed against a higher risk of side effects, the main one being rash, including serious cutaneous reactions, and the risk of incurring drug resistance, which theoretically could compromise future treatment attempts, in case of failure. Rash events are in most cases mild to moderate, and also the severe cases generally remit after discontinuation of telaprevir. It is recognised that a handful of severe cutaneous adverse reactions were seen during the program, though no deaths. This remains an important risk associated with telaprevir therapy. However, a number of measures are foreseen to mitigate the risk as reflected in the Risk management plan; these include close monitoring of dermatological safety profile of telaprevir and a physician educational programme aimed at advising physicians on the management of rash and severe cutaneous reactions. In addition appropriate warnings are instituted in the SmPC. Overall the risk of severe rash/serious cutaneous reactions does not outweigh the benefit of greatly increased SVR rates. Regarding the risk associated with selection of resistance, this only pertains to patients that fail telaprevir-based therapy. Such patients would not have reached SVR with the present standard of care. Available data indicate that in most cases there is a reversion to wild-type after discontinuation. Even if there in fact would be consequences for retreatment due to resistant variants selected during telaprevir therapy, this does not outweigh the benefit of the increased SVR rates with telaprevir.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of INCIVO in the treatment of chronic hepatitis C is favourable and therefore recommends the granting of the marketing authorisation.

1.12. Jevtana

Benefits

- Beneficial effects

Jevtana is intended for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen in combination with prednisone or prednisolone. In such a population, the goal of the treatment is to improve the overall survival or at least the quality of life. The present submission is based on one single pivotal study. The primary objective was to determine whether cabazitaxel/Prednisone could improve overall survival when compared to mitoxantrone/prednisone. cabazitaxel/Prednisone was associated with a 2.4 month increase in median overall survival compared to mitoxantrone/prednisone.

- Uncertainty in the knowledge about the beneficial effects

Secondary endpoints such as PFS, tumour response rate and tumour progression were consistent with the primary endpoint. In secondary analyses, a median PFS difference of 1.4 month in favour of cabazitaxel/prednisone was also observed. cabazitaxel/prednisone was also associated with higher response rate and increased time to PSA progression. However, these parameters have inherent limitations due to, among others, ascertainment bias, inter-observer variability and the fact that no independent review of PFS assessment was carried out.

There is some uncertainty about the efficacy in patients that had received less than 225 mg/m^2 of docetaxel. Previous treatment with <225 mg/m^2 cumulative dose of docetaxel was introduced as an exclusion criterion after protocol amendment. A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in JEVTANA arm, 30 patients in mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR (95%CI) 0.96 (0.49-1.86)). This observation may be due to a lower efficacy in this subgroup due to different patient or disease characteristics. The low number of patients in this subgroup analysis may also explain the lack of a clear effect. Thus, although there is insufficient evidence to conclude that the benefits are lacking in this subgroup, this information has been included in the SmPC (see section 5.1) to help make an informed treatment choice.

Risks

- Unfavourable effects

The number of patients with any TEAE, serious TEAE, grade ≥3 TEAE and withdrawals due to any TEAE were significantly higher in the cabazitaxel group compared to mitoxantrone. In study EFC6193, the percentage of patients who died from TEAEs (other than progressive disease) within 30 days of last infusion was 4.9% in the cabazitaxel group compared with 1.9% in the mitoxantrone group. Of the 18 patients who died in the cabazitaxel group, 7 of these were attributed to neutropenia and its consequences. The haematological toxicity was also higher for cabazitaxel/predinsone compared to

mitoxantrone/prednisone. In Study EFC6193, the incidence of Grade ≥ 3 neutropenia was higher with cabazitaxel than with mitoxantrone (27.5% *vs.* 8.4%), with notably more febrile neutropenia in cabazitaxel group. In addition, infections were more frequent in the cabazitaxel arm compared to mitoxantrone arm. Even with prophylactic or therapeutic G-CSF, cabazitaxel was associated with a higher rate of neutropenia leading to infections and sepsis.

- Uncertainty in the knowledge about the unfavourable effects

As might be expected in the Phase II study, the side effect profile for the < 25mg/m² dose was generally more favourable when compared to the ≥25mg/m² dose. It is unclear whether the <25mg/m² dose would have similar activity to the ≥25mg/m² dose but with a more acceptable safety profile. The Applicant has submitted the protocol of a randomised, open label study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² in second line mHRPC patients.

No direct comparison to other taxane therapies has been performed by the applicant.

Benefit-risk balance

- Importance of favourable and unfavourable effects

The single most influential factor is considered to be the improvement in median overall survival. The pivotal study submitted met both primary and secondary endpoints with the exception of pain response. More subjects experienced an adverse event, a related adverse event or a treatment related death in the cabazitaxel arm. Neutropenia and in particular febrile neutropenia is an important treatment-related side-effect associated with cabazitaxel/prednisone.

- Benefit-risk balance

The CHMP is of the opinion that there is a clear benefit in terms of overall survival associated with cabazitaxel/prednisone compared to mitoxantrone/prednisone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. In a subgroup of patients that received previously less than 225 mg/m^2 of docetaxel, the benefit in OS is not significant, and the information has been added in section 5.1. Despite the increased toxicity associated with cabazitaxel/prednisone, an advantage in overall survival was observed and the effect in terms of this endpoint was considered to be clinically and statistically significant.

Discussion on the benefit-risk balance

The effect in terms of overall survival is similar to what has been observed with other therapies in late line cancers, where dramatic effects in terms of overall survival are rare due to the advanced stage of the disease. Due to the poor prognosis, high unmet clinical need and lack of alternative therapies, the observed benefits in terms of overall survival are considered clinically important. There are no major remaining uncertainties that have an impact on the benefit-risk balance.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Jevtana in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen was favourable and therefore recommended the granting of the marketing authorization.

1.13. Nulojix

Benefits

- Beneficial effects

Belatacept represents a new therapeutic principle for basal immunosuppression, co-stimulatory blockade, in the prevention of graft rejection after renal transplantation. It lacks the nephrotoxic adverse effects of calcineurin inhibitors that are now the cornerstones of short time as well as long time immunosuppression after organ transplantation. Consequently, belatacept could potentially provide better long time transplant function, measured as glomerular filtration rate and, in a prolonged time perspective, give less chronic allograft nephropathy and thereby also a better long time renal graft survival. As it is a protein, a fusion of a modified Fc domain of human IgG1to the extracellular domain of human CTLA-4, it does not seem to interact with any of the enzyme systems of the liver, making pharmacokinetic interaction less probable.

As belatacept is administered intravenously once a month, it gives possibilities for a better control of patient adherence to therapy. Another benefit is that therapeutic drug monitoring does not seem to be required.

To establish the clinical value of a new immunosuppressive agent with properties hypothesised for belatacept, clinically relevant superiority in renal function relative to the existing alternatives without a detrimental effect of subject and graft survival should be demonstrated.

In pivotal clinical studies, belatacept in the applied low intensity dosing regimen was shown to be non-inferior to ciclosporin for the primary composite endpoint of patient and graft survival at 12 months, in a low risk transplant population (96.5% vs 92.8% subject or graft survival for belatacept and CsA, respectively, 97.3% CI: -1.1; 9.0) as well as in a high risk transplant population (88.0% vs 84.8%, 97.3% CI: -5.0; 11.4). At 36 months, the results for patient and graft survival the belatacept treated groups remained non-inferior to ciclosporin in the low risk study population (92.2%, 92.0%, and 88.7%), as well as in the high risk study population (80.4%, 82.3%, and 79.9", respectively).

In the low risk transplant population, belatacept was significantly superior to ciclosporin for the composite co-primary endpoint proportion of patients with GFR <60 at 12 months or a decrease in GFR>10 between month 3 and 12 (54.2% vs 77.9%, 97.3 CI: -33.3; -13.7)), while in a high risk transplant population the effect was less pronounced and did not reach formal statistical significance for the applied low intensive belatacept regimen (76.3% vs 84.8, 97.3% CI: -18.0; 0.9). However, in both studies the mean difference in calculated GFR tended to increase during the 36 month follow-up. The positive effects on renal function were shown to be sustained up to 36 months in both pivotal studies. Both belatacept treatment arms had better results for GFR than patients in the ciclosporin treatment arm in the low risk patient study IM103008, the difference between treatment arms was independent of where the cutoff point was applied, between 45 and 75 ml/min. The difference between treatments, in favour of belatacept, was also seen in the high risk patient study IM103027 but this difference was much less between treatment arms in the latter study.

A trend towards a lower prevalence of chronic allograft nephropathy (CAN) was demonstrated in the low risk study (23.9% vs 32.4%, 97.3% CI: -17.9; 0.9) and in the high risk study, although less pronounced, (46.0% vs 51.6%, 97.3% CI: -17.2; 6.0).

- Uncertainty in the knowledge about the beneficial effects

Non-inferiority was demonstrated for the composite endpoint of patient and graft survival in both pivotal studies, in spite of more episodes of acute rejection with belatacept treatment.

With respect to renal function, convincing positive effects on glomerular filtration rate and prevalence of chronic allograft nephropathy were observed in the low risk study only while no significant effects in the high risk study with patients and donors more representative for renal transplant centres in general. The effects were sustained during a 36 month study period but was more evident in a low risk patient population than in a high risk patient population. Nevertheless, patients in study IM103027 still achieved an approximately 35% higher calculated GFR than patients in the CsA group (compared to an approximately 45% higher calculated GFR for patients on belatacept as compared to CsA-treated patients, in study low risk study IM103008). Even the smaller difference between treatment groups in study IM103027 is considered as a clinically meaningful difference.

Whether the better renal function at 3 years this will also translate into a better all over survival time of renal transplants on belatacept in the very long run remains to be proven.

There were more acute rejections on belatacept treatment during the first 12 months, especially in the low risk study. Although the excess of early acute rejections on belatacept treatment did not seem to have a detrimental impact on the overall patient and graft survival or on renal function at 36 months, it should be considered that it may increase the need for renal biopsies, hospital care and additional immunosuppressive treatment for patients treated with belatacept.

Results from pivotal studies hint that the cardiovascular risk profile of belatacept seems to be better than that of calcineurin inhibitors but a final evaluation of a possible advantage in this area will have to await larger and more targeted long-term studies.

Risks

- Unfavourable effects

Major deficiencies were identified in the documentation supporting the proposed system for in-process control of the drug substance and further documentation was provided to assure that comparability between commercial product and product used in clinical studies.

The selection of these tests is generally considered appropriate, as they cover most of the observed or expected variability. There were, however, concerns raised on the performance of some of the analytical methods. In process of this procedure, the control in performance of analytical methods has been improved and is largely considered acceptable. However, some concerns remain related to the B7 bioassay and the SDS-PAGE analysis. Although these analyses are considered acceptable for confirmation of consistency in production using the currently established and validated process, they do not hold acceptable standard for analytical procedures to be used for demonstration of comparability of product in conjunction with future introduction of major changes in the commercial production process. The applicant is therefore requested to perform optimisation/validation studies to further improve the control of biological activity and purity in analysis by the B7 bioassay and the SDS-PAGE analysis.

The size of the safety data base and the exposure over time is acceptable for an application for a new immunosuppressive regimen in renal transplantation.

Belatacept, like other immunosuppressives, increases the risk of malignancies and infections (these risks are addressed in the SmPC and in the RMP). However there are clear indications that the belatacept based regimens are associated with some specific safety issues that warrant further evaluation and discussion. Posttransplant lymphoproliferative disease, PTLD, was significantly more common with belatacept than with ciclosporin, especially in EBV-negative graft recipients, and these cases have a bad prognosis with high mortality. A remarkable proportion of the PTLDs were localised in the CNS, a localisation otherwise very rare for this kind of disease. The mechanism behind this unusual

localisation is unknown, as there are no data making plausible that belatacept should be able to cross the blood brain barrier. The risk of PTLD is addressed in the SmPC and the RMP. In clinical studies there were two cases of the very rare and lethal disease of PML (this risk is addressed in the SmPC and the RMP).

Other infections that were more common in belatacept treated patients than in the control group patients were infections with viruses from the herpes virus family, polyoma virus infections and tuberculosis. These risks are addressed in the SmPC and in the RMP.

Furthermore, graft thromboses were more common with the belatacept based regimens than with cyclosporine in one of the pivotal studies with high risk recipients and high risk donors.

In a phase 2 liver transplantation study, with immunosuppressive regimens different from those used in pivotal studies with belatacept for the renal transplantation indication applied for, and with a higher dose of belatacept, an increased incidence of infections and an increased mortality was seen. This is in contrast to renal transplant studies, where there was no increased mortality in belatacept treatment groups at 36 months in pivotal studies. The increased mortality on belatacept in the liver transplant study is most likely due to overimmunosuppression. A warning against the use of belatacept in liver transplantation has been introduced to section 4.4 of the SPC, information on the liver transplant study has been amended to section 5.1, and the RMP has been updated with respect to off label use of belatacept in liver transplantation. Complete study data from the extension of the liver transplantation study IM103045 will be submitted for evaluation as soon as they are available.

- Uncertainty in the knowledge about the unfavourable effects

The CHMP initially raised the potential of belatacept to block the inhibitory receptor CTLA-4 thereby enhancing the immune response. This has been adequately addressed through re-assessment of the available *in vivo* or clinical data hence the potential issue of immune enhancement was considered resolved. Autoimmunity is identified as an important potential risk in the RMP, with enhanced pharmacovigilance activities.

As antibody formation, also of neutralising antibodies, was very frequent in healthy volunteers, there is a fear that antibodies to belatacept could be more common in patients on a low basal immunosuppression or in patients resuming belatacept therapy after a prolonged pause between infusions. Such antibodies could possibly cause allergic reactions or autoimmunity and possibly impair the therapeutic effect of belatacept. From aspects of immunogenicity and antibody development, efficacy and safety of belatacept in the retreatment situation have not been fully clarified, especially in the situation when belatacept is restarted after a prolonged period of time, with or without continued other immunosuppression. Therefore, a warning against retreatment has been added to section 4.4 of the SmPC and these safety concerns have been adequately addressed in the RMP.

Further assessment to rule out immunogenicity is needed and the RMP has been updated with a plan designed to improve the understanding of the relationship between antibody development and peri-infusional events within the clinical trials.

In addition, preclinical data shows that belatacept has a negative impact on the developing immune system and should therefore not be used in later phases of pregnancy. Thus, pregnancy would lead to a recommendation to change to another treatment regimen. It is not clear how to handle a woman that becomes pregnant during belatacept treatment and whether belatacept treatment can safely be resumed after pregnancy and childbirth or not. Therefore, a warning related to pregnancy and lactation has been added to section 4.4 of the SmPC and this safety concern has been addressed in the RMP.

Even if EBV-negative or unknown transplant recipient status is a contraindication for belatacept, PTLD remains as a risk in the Risk Management Plan and will be monitored in postapproval studies.

Benefit-risk balance

- Importance of favourable and unfavourable effects

The need for new effective immunosuppressant lacking the adverse nephrotoxic and cardiovascular effects of calcineurin inhibitors is great. Therefore, the positive effects of belatacept in terms of 1- and 3-year patient and graft survival and of renal function at 1, 2 and 3 years are important.

The increased number of acute rejections with belatacept did not impair the efficacy or safety of in a 36 month perspective and is therefore considered not to have a severe impact on the risk benefit balance for the product.

The observed increased incidence of posttransplant lymphoproliferative disease with severe prognosis and often lethal outcome is a safety concern as are the PML cases. These observations could indicate increased risks that are carefully dealt with in the SmPC and in the RMP. Belatacept is contraindicated in EBV-negative patients. The observed increased risk for other infections such as herpes virus and polyoma virus infections and tuberculosis will be managed with appropriate risk minimisation activities.

Further assessment to rule out immunogenicity is needed and the RMP has been updated with a plan designed to improve the understanding of the relationship between antibody development and peri-infusional events within the clinical trials.

Safety findings from the phase 2 liver transplantation study are at this stage considered to be confined to liver transplantation, as no increased mortality with belatacept was seen up to 36 months in the renal transplant studies. The total immunosuppressive burden in the liver transplant study was heavier than in the renal transplant studies. Liver transplantation patients are subjected to more complicated and extensive surgery than renal transplant patient but in general have less need for immunosuppression than the renal transplant population.

- Benefit-risk balance

The overall benefit of belatacept has been sufficiently demonstrated up to 36 months. The demonstrated benefits are considered to outweigh the identified and potential risks. The overall benefit-risk balance of Nulojix is positive.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Nulojix "in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant (see section 5.1 for data on renal function). It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen" was favourable and therefore recommended the granting of the marketing authorisation.

1.14. Trajenta

Benefits

Beneficial effects

Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor that lowers blood glucose levels by augmenting the glucose-stimulated insulin release through increased levels of endogenous GLP-1.

Efficacy and safety of linagliptin were studied in phase II/III studies, comparing the effects of linagliptin with placebo

-as monotherapy in general (1218.16),

-as monotherapy in patients intolerant for metformin (1218.50)

-as add-on to metformin (1218.17 and 1218.20)

-as add on to sulphonylurea ((1218.35)

-as initial combination therapy with pioglitazone (1218.15)

-as triple therapy with sulphonylurea and metformin (1218.18).

Additional relevant efficacy and safety data were obtained from the following phase II studies

- (dose finding) monotherapy study 1218.5 (internal control metformin)

- (dose finding) add-on to metformin study 1218.6 (internal control glimepiride)

- monotherapy study in patients with severe renal insufficiency (1218.43)

- linagliptin dual combination therapy with metformin (1218.62)

All submitted studies are placebo-controlled except for study 1218.20, which used glimepiride as active comparator. Pivotal efficacy studies are 1218.15, 1218.16, 1218.17 and 1218.18. However, the results of study 1218.15 (combination with pioglitazone) did not support an indication. The large active-controlled study 1218.20 is also considered important

In all studies, treatment with 5 mg linagliptin once daily resulted in a statistically significant decrease of HbA1c, the primary efficacy endpoint. In comparison to placebo, linagliptin resulted in an overall decrease in HbA1c of approximately 0.6%. However, in Caucasian or European patients, the target population of this application, the treatment effects were consistently smaller than in Asian patients. Similarly, efficacy results differed across geographical regions. However, when the results on European patients were confined to the EU population in an additional pooled subgroup analysis, the placebo-adjusted treatment effects of linagliptin were more pronounced than in non-EU patients.

In monotherapy, linagliptin showed relevant efficacy in European patients in the pivotal study 1218.16 (-0.52%). A slightly lower effect was achieved in the monotherapy dose-finding study 1218.5 (-0.46). In the supportive study 1218.50 in patients with intolerance to metformin, the placebo-adjusted difference in the European population was -0.15%. However, the effect in the Caucasian population was similar to results in study 1218.16 (placebo-adjusted difference: -0.43). In addition, in the supportive study 1218.05 the placebo-adjusted treatment difference was -0.50 in Caucasians.

In dual combination therapy with metformin a relevant placebo-adjusted decrease in HbA1c was found (-0.51%) in European patients of study 1218.17, supported by a change of –0.73% in the dose-finding

study 1218.6. In addition, the new study 1218.62 demonstrated a placebo adjusted treatment effect of linagliptin in combination with metformin in Caucasian patients (-0.69 for 2.5 mg bid; and -0.66 for 5 mg qd).

When linagliptin was added to SU in dual therapy the placebo-adjusted effect on HbA1c in European patients was small, ie. -0.29%, and not considered clinically relevant.

The efficacy of linagliptin in combination with pioglitazone was investigated as initial combination therapy with about 50% of enrolled patients being treatment naive. Linagliptin treatment resulted in European subjects in a relatively small placebo-adjusted decrease in HbA1c of -0.37%.

Linagliptin therapy in triple combination with metformin and SU resulted in an adjusted treatment effect in European patients of -0.47%.

The treatment effect of linagliptin in terms of adjusted mean differences to placebo in HbA1c was similar in patients with normal renal function (-0.61%), and patients with mild (-0.63%) or moderate (-0.57%) renal impairment. In the separate trial in patients with severe renal insufficiency (1218.43) the adjusted mean difference to placebo in HbA1c after 52 weeks was -0.72%.

Linagliptin was largely weight neutral except in the combination with pioglitazone where it aggravated the pioglitazone- induced weight gain for unknown reasons. A beneficial effect on weight was observed compared to glimepiride in study 1218.20 with a treatment difference of -2.49 kg at week 52.

Linagliptin also was associated with a markedly lower frequency of hypoglycaemia compared to glimepiride (overall frequencies 5.4% vs. 31.8%). This included hypoglycaemic events with blood glucose levels below 54 mg/dL (9.5% vs. 33.1%) and severe hypoglycaemic events (2.4% vs. 3.6%), although the number of severe events was low (1 vs. 9).

Uncertainty in the knowledge about the beneficial effects

Linagliptin has been shown to be effective as monotherapy in patients with intolerance to metformin, in patients with renal insufficiency that are not candidates for treatment with metformin, and as add-on treatment with metformin or with metformin + SU. However, linagliptin has not been shown to be an effective treatment in European patients as add-on to SU and add-on to pioglitazone. In addition, the design of the add-on to pioglitazone trial was not appropriate, as at least 50% of patients in the study were not failures on pioglitazone monotherapy.

Regional/racial differences in treatment response have been observed with the smallest effect of linagliptin seen in European patients. In PK studies, peak and total exposure were about 30% higher in Japanese and Chinese subjects than in Caucasian subjects. However, the median and mean level of DPP-4 inhibition was similar in the different races. Therefore, the cause of the regional/racial differences remains unclear, but treatment differences between the EU and non-EU population within Europe may best be explained by differences in pre-study diabetes care.

In the active comparator study (1218.20) both active treatments resulted in a decrease of HbA1c from baseline. However, non-inferior efficacy of linagliptin compared to glimepiride has not been convincingly demonstrated in this study. The impression that efficacy of linagliptin is not similar to that of glimepiride is supported by new data from the second part of study 1218.50, where glimepiride vs. linagliptin induced a mean decrease in HbA1c of 0.82% vs. 0.44%.

The finding of a lower number of hypoglycaemic events with linagliptin compared to glimepiride is an advantage and expected from the known mechanisms of action of these drugs. However, the observed beneficial effect of linagliptin may be overestimated considering the smaller glucose-lowering effect of linagliptin (leading to smaller HbA1c and FPG reduction).

Very elderly patients and patients with hepatic impairment have not been investigated in sufficient numbers.

Risks

Unfavourable effects

The safety database is considered large enough to sufficiently characterize the AE profile of linagliptin. The main basis for safety assessment was the SAF2 (N=3749, including all placebo-controlled trials with linagliptin 5mg). The incidence of adverse events with linagliptin was mostly comparable to placebo and active comparator groups, and the safety profile appears comparable with other DPP-4 inhibitors. Linagliptin appears to be tolerated relatively well in terms of gastrointestinal complaints. One of the adverse events consistently associated with linagliptin was an increased incidence of hypoglycaemia. This effect was small when linagliptin was used in monotherapy or in combination with metformin and was more pronounced when linagliptin was added to a background treatment of metformin and sulfonylurea, but was not always considered causally related and medical assistance was only required in a small percentage of the patients. Increase in hypoglycaemic events in association with insulin secretagogues is also known for other antihyperglycaemic drugs that *per se* have low propensity to cause hypoglycaemia. This issue is appropriately reflected in the SmPC.

Similar to other GLP-1 based therapies, linagliptin may be associated with an increased risk of pancreatitis, although this did not appear to be an important problem in the presented trials. The relevance of the higher frequency of skin and subcutaneous tissue disorders in the linagliptin group is unknown. Other DPP-4 inhibitors have also been associated with skin reactions during preclinical studies in animals. In addition, skin exfoliation (n=5) and exfoliative dermatitis (n=1) were observed only in the linagliptin group. These issues of pancreatitis and skin reactions are adequately addressed in the SmPC and RMP and should be monitored further post licensing.

Linagliptin was consistently (AEs and ADRs and across studies) associated with a slightly enhanced incidence of muscle pain. CK increases were not observed and most of the AEs were mild. Thus, musculoskeletal AEs are not regarded as a relevant concern.

Although linagliptin generally was weight-neutral, it aggravated the pioglitazone-induced weight gain (+2.4 vs. +1.2kg for linagliptin+pioglitazone vs. pioglitazone, respectively; see study 1218.15) which may be unfavourable in respect to CV risk. The cause of the observed weight gain is unclear, but for several reasons, an indication for linagliptin in combination with pioglitazone is not acceptable.

For patients with moderate renal impairment in the placebo controlled trials, a higher overall incidence of adverse events was observed in the linagliptin group (50.0% placebo vs. 65.2% linagliptin, respectively). Therefore, linagliptin should be used with care in these patients. Patients with severe renal insufficiency were investigated in a separate trial. No major difference in AE incidence between the linagliptin and the placebo group was observed in general (94.1% linagliptin vs. 92.3% placebo, respectively). All AEs belonging to the term "renal impairment" were more frequent in the linagliptin (16.2% linagliptin vs. 6.2% placebo, respectively), but the absolute numbers were small. On average, renal function measured as eGFR was not influenced by linagliptin.

Uncertainty in the knowledge about the unfavourable effects

As discussed above under safety, the current information of linagliptin on CV risk is limited. The nature of the cardiovascular AEs with increased incidence under linagliptin was consistently related to hypertension and heart rate. On average, no increase in blood pressure or heart rate was observed in SAF-2. The results of a dedicated meta-analysis of cardiovascular events based on independent

adjudication are difficult to interpret as confidence intervals are wide and data on high-risk patients limited. The available data, including comparison with active comparators (voglibose, glimepiride), did not indicate an increased risk, and there is no suspicion of a detrimental effect. These results, however, were largely dominated by the relatively high number of CV events in patients treated with glimepiride. In addition, the low incidences of cardiovascular disease in the trials reflect the fact that patients with more severe pre-existing CV disease were not included in the studies. Nevertheless, the absence of an increased cardiovascular risk is in line with other DPP-4 inhibitors, where the assessment of CV risk also had its limitations. The applicant has indicated that a follow-up study including patients with high CV risk (study 1218.63) recently started.

Death rate with linagliptin (incidence rate 1.9) was higher in comparison to placebo (incidence rate 0) but numbers were very small and data are inconclusive.

The number of patients with hepatic impairment being treated with linagliptin was too low to yield any relevant information in a subgroup analysis. Its use cannot be recommended. Very elderly patients (>75 yrs) have also not been investigated in sufficient numbers. Therefore currently, the use of linagliptin cannot be recommended in these populations.

Phototoxicity did not occur during treatment with linagliptin. However, the individual study reports describe 4 patients with photosensitivity with linagliptin. The seriousness of these adverse events caused by linagliptin was mild to moderate. The 2 cases of angioedema that occurred in the linagliptin group may be due to co-medication. These issues are mentioned in the SmPC.

The increased incidence of hypoglycaemia in combination with SU and metformin is not surprising. Other gliptins have also been associated with this problem when combined with SU derivatives as also indicated in their SmPCs. Thus, this problem has also been addressed in the SmPC of linagliptin.

The higher incidence of infections has also been described with other DPP-4 inhibitors. The DPP-4 inhibitors may be relatively specific for GLP-1, but the long-term consequences of DPP-4 inhibition and its effects on other DPP-4 substrates, particularly with respect to immune function, are unknown. Although the increased incidence of infections with linagliptin was relatively small in comparison to placebo (19.1% vs. 20.6%) and linagliptin was not associated with a decrease in absolute lymphocyte count, it is important to realize that these observations were done in relatively short term trials, and potential long term effects remain a concern. This should be monitored closely post marketing, an issue that has been addressed in the risk management plan.

The safety assessment after co-administration with the potent CYP 3A4/P-gp inhibitor ritonavir demonstrated that the total exposure of linagliptin was increased. However, this is not expected to affect safety.

Benefit-risk balance

Importance of favourable and unfavourable effects

The most important favourable effect of linagliptin is lowering of the HbA1c. This effect appears relatively small in comparison to the effects of other drug classes, such as metformin, insulin and SU preparations. The treatment response (HbA1c) was generally lower in European/Caucasian patients compared to Asian patients. When the results were confined to the EU population in an additional pooled analysis, the placebo-adjusted treatment effects of linagliptin were more pronounced providing further reassurance that linagliptin is an effective treatment in the population applied for.

Linagliptin's additive effect to non-responders to SU derivatives is currently questionable. The effect on HbA1c was -0.29% in the European population. This is considered too small for justifying an indication.

In addition, add-on treatment to pioglitazone has not been appropriately investigated as the study design is not considered appropriate. CHMP guidance for add-on trials, requests that the new antidiabetic agent should be added in non-responders to the established antidiabetic agent. In this trial 50% of patients were drug-naïve, and therefore not non-responders. Considering the relatively small effect size (-0.37% decrease in HbA1c) and the increased weight gain the B/R ratio of this dual combination therapy appears unfavourable.

The effects of linagliptin and glimepiride are not considered similar. Non-inferior efficacy of linagliptin compared to glimepiride has not been demonstrated sufficiently. Therefore, no statements were included in Section 5.1 of the SmPC.

The use of linagliptin in monotherapy as alternative to metformin is considered acceptable in patients that cannot take metformin due to gastrointestinal intolerance or in patients with contraindications to metformin due to renal impairment.

Linagliptin has a primarily non-renal route of excretion. This is an advantage of linagliptin in patients with moderate to severe renal insufficiency. For patients with renal insufficiency, efficacy in subgroup analyses as well as separate trial 1218.43 seems adequate. No major difference in AE incidence between the linagliptin and the placebo group was observed in general, but currently it cannot be fully excluded that linagliptin increases the incidence of infections and causes worsening of renal function under certain circumstances. These issues will be followed as potential risks in the RMP.

The finding of a lower number of hypoglycaemic events with linagliptin compared to glimepiride is an advantage and expected from the known mechanisms of action of these drugs. However, the beneficial effect of linagliptin may be overestimated considering the apparently smaller glucose-lowering effect of linagliptin (leading to smaller HbA1c and FPG reduction). Due to the presence of insulin resistance, hypoglycaemia, especially severe hypoglycaemia is usually not a major problem in patients with T2DM. However, (very) elderly patients are generally more prone to experiencing hypoglycaemia. Due to its mechanism of action, linagliptin is not associated with hypoglycaemia except when used in combination with a SU but the enhancement of SU-associated hypoglycaemia is also known for other antihyperglycaemic drugs and is therefore not unique to linagliptin. The low propensity of linagliptin to cause hypoglycaemia is an advantage that may be relevant in patients more prone to hypoglycaemic events.

Linagliptin is largely weight-neutral, except when given in combination with pioglitazone where it was shown to aggravate pioglitazone-induced weight gain (+ 2.4kg vs. +1.2 kg). On the other hand, linagliptin provides a weight advantage compared to SUs (-2,5 kg), which can be considered beneficial in the usually overweight/obese patients with T2DM.

Efficacy and safety are currently insufficiently investigated in certain subgroups, such as very elderly patients (>75 yrs), and patients with hepatic impairment. Linagliptin does not appear to be related to an increased cardiovascular risk, but absolute numbers of CV events were very low. The possible increased risk of infections, skin reactions, and pancreatitis is also important, but it should be acknowledged that these possible side effects have also been associated with other DPP-4 inhibitors and they will be monitored according to the RMP. Additional, potentially new safety issues, in particular photosensitivity and angioedema have been addressed in the SmPC.

Discussion on the benefit-risk balance

Although overall, linagliptin provided statistically significant glycaemic improvement, the treatment response (HbA1c) was generally lower in European/Caucasian patients compared to Asian patients.

When the results in Europeans were confined to the EU population in an additional analysis, the treatment effects of linagliptin were somewhat more pronounced.

As dual therapy with metformin, and as triple therapy with metformin and SU, a clinically relevant effect was obtained. However, the effect of linagliptin appeared smaller compared to glimepiride, and non-inferiority in patients treated with metformin was not demonstrated sufficiently and a respective statement in the SmPC cannot be accepted.

The treatment effects of linagliptin in dual combination with SU and with pioglitazone appear too small to justify an indication. Its use as monotherapy as alternative to metformin is appropriate in those patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

Lack of data or availability of limited data on certain subgroups (i.e. hepatic insufficiency, very elderly) has been resolved by appropriate wording in the SmPC. More information on cardiovascular safety with linagliptin is important and will be investigated post-marketing in the ongoing CV safety study, as described in the RMP. Several possible side-effects were identified, but the risks were only mildly elevated in comparison to placebo and comparators. Targeted follow up of adverse events of interest in the RMP may be sufficient.

In conclusion, the benefit-risk of linagliptin for the claimed indication of the treatment of patients with type 2 diabetes mellitus, to achieve glycaemic control in dual combination with SU or with pioglitazone is considered negative.

The benefit-risk of linagliptin for the claimed indication of the treatment of patients with type 2 diabetes mellitus, to achieve glycaemic control in monotherapy is acceptable as an alternative to metformin in patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

The benefit/risk of linagliptin is also considered positive for linagliptin in dual combination with metformin or in triple combination with metformin and a SU, when this treatment, together with diet and exercise, does not provide adequate glycaemic control.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Trajenta in the treatment of

"type 2 diabetes mellitus to improve glycaemic control in adults:

as **monotherapy**

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

as **combination therapy**

- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control."

is favourable and therefore recommends the granting of the marketing authorisation.

1.15. Trobalt

Benefits

Overall the epilepsy development programme of retigabine provides evidence of efficacy in partial onset epilepsy as add-on therapy. This evidence is primarily based on one phase IIB trial (study 205) and two phase III trials (studies 301 and 302), which combined randomized 1244 subjects, 427 to placebo and 813 to three dose regimens of RTG of 600, 900 and 1200 mg daily respectively.

- Beneficial effects

It is acknowledged that there is a high medical need in the partial epilepsy patient population. Based on the integrated analysis and concerning the primary endpoint of responder rate during the maintenance phase, statistically significant superiority to placebo was demonstrated across all three dose regimens, but this was consistent only for the 1200 mg daily dose regimen, whereas superiority to placebo was shown for the two other regimens in one of the studies (302), but not in the other (205). There was a dose response effect with responder rates of 28-39% (600 mg), 40-47% (900 mg) and 41-55% (1200 mg), compared to 19-26% for placebo. For the original primary endpoint of median percent reduction in seizure frequency in study 205, superiority to placebo was demonstrated for the 900 mg and 1200 mg regimens, but not for the 600 mg. Efficacy of retigabine in the PCTs is within the range defined by similar studies of other new AEDs as add-on therapy in refractory epilepsy.

- Uncertainty in the knowledge about the beneficial effects

The Study 205 differed somewhat from studies 301 and 302 with regard to study design, inclusion criteria and the formulation of trial medication. Integration of efficacy results across studies was achieved by post-hoc analysis in study 205, in which the per protocol primary endpoint was different from the primary endpoints in studies 301 and 302.

The unique pharmacologic mechanism of action of retigabine (first-in-class M-current potassium channel opener) does not – in itself – add positively to the benefit-risk balance unless accompanied by clinical data that point to a unique effect not accomplished with other AEDs. However, the Applicant has provided data indicating that retigabine is efficacious even in patients with inadequate seizure control on two or more AEDs.

Risks

- Unfavourable effects

Several safety issues were identified with a dose dependent pattern as their most common feature.

Retigabine treatment was associated with an increase of frequent CNS related adverse events, occurrence of visual hallucinations and psychotic disorder exclusively in the RTG treatment groups, and frequent, and in some cases serious, renal and urinary tract symptoms. There was lack of sufficient data to assess teratogenicity in humans. Other safety issues emerging from the preclinical pharmacology studies, apart from general CNS signs, were a reduction of smooth muscle contractility affecting urinary and gall bladder function, and a probable interaction with thiopental, contrary to other anaesthetic agents.

CNS related adverse events, such as dizziness, somnolence and fatigue were frequent and dose dependent. Occurrence of adverse events impacting on cognitive function, like memory and attention impairment was high and adverse events of particular importance for daily life activities such as balance/gait disturbance and language were also frequent.

Hallucinations and psychosis were also dose related, and visual hallucinations and psychosis were only reported with retigabine but not with placebo.

Renal and urinary tract related adverse events were frequent and dose related. Nephrolithiasis was reported in 4 cases occurring all in the 1200 mg RTG group. Serious urinary retention was irreversible in one case, requiring intermittent self-catheterization.

The majority of CNS and urinary adverse events not leading to withdrawal disappeared during the course of the studies. About one quarter disappeared after one week and about half after one month.

Retigabine treatment was associated with a modest increase of QTc interval in a dose dependent manner. The clinical significance of this finding is uncertain. However, in SmPC section 4.4, Special warnings and Precautions for use, warnings have been introduced, and it is recommended that an ECG is recorded in patients at risk before initiation of treatment and in those with a corrected QT interval >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. With the modest QTc increase observed, it is considered disproportionate to require recommendations of baseline ECG for all patients.

Serious cardiac events were identified in subjects on retigabine. Among others, these events included cardiac arrest/asystole and transient non-sustained ventricular tachycardia. However, in the pivotal clinical trials there does not appear to be any pattern in cardiac AEs observed with retigabine when compared with placebo.

RTG treatment discontinuation related to TEAEs, ranging between 17.4 and 31.3%, was higher than in the placebo group (10.5%), and clearly dose dependent. In addition TEAE related RTG discontinuation rates are higher than those reported in clinical trials with most other AEDs marketed during recent years.

- Uncertainty in the knowledge about the unfavourable effects

Retigabine and other AEDs share many of the same safety and tolerability problems, especially with respect to CNS effects. The Applicant has not provided additional documentation to counter the impression from the comparisons made to other AEDs that retigabine belongs to the category of AEDs with the most frequent CNS as well as other adverse events. It is agreed that in many instances the tolerability issues associated with retigabine may be manageable by slowly titrating/adjusting the dose or discontinuing the medication and shifting to another – as is the case with other AEDs.

A limited amount of data is provided on persons aged ≥ 65 years, a population subgroup relevant for the clinical scope of RTG. Additional safety and tolerability data were provided in 89 elderly patients (61 on retigabine) with post herpetic neuralgia (PHN), but with a lower dosage and shorter time of exposure than in the epilepsy programme. A poorer tolerability in the elderly compared with the younger population, in particular with regard to CNS and urinary events was suggested. The predominance of nervous system and psychiatric events, which are noteworthy in this age group that is often fragile, especially with regard to CNS adverse effects. However, appropriate strengthening and additions have been included in the SmPC text to address these concerns.

The risk of SUDEP with RTG treatment was lower than that with placebo and was within the range of SUDEP rates published in the literature, but it was much higher than SUDEP rates reported for population based epilepsy cohorts. Overall, the figures were small and firm conclusions were not easy to draw.

Benefit-risk balance

- Importance of favourable and unfavourable effects

A high medical need in the partial epilepsy patient population is undisputed, and evidence of efficacy of retigabine in patients with partial onset epilepsy as add-on therapy has been provided.

The forced titration regimens used in the clinical studies may have resulted in more pronounced tolerability problems compared to the individual titration based on each patient's efficacy and tolerability used in normal clinical practice. This is likely to result in an overestimation of adverse events compared to clinical conditions outside a study protocol where doses are likely to be titrated in a more lenient way. However, this would also be the case for adverse events rates reported from other studies with other AEDs employing forced titration regimens.

- Benefit-risk balance

Overall, there is robust evidence for a significant and clinically relevant effect of the retigabine 1200 mg/day dose. There is also evidence for significant and clinically relevant effect of the 900 mg/day dose, but this is less consistent. The effect of the 600 mg/day dose is less consistent compared to the two higher doses. The efficacy results are observed even in patients with a background treatment of two or more AEDs, i.e. patients who must be categorised as quite resistant to treatment.

As discussed above, a multitude of adverse events (in particular related to CNS and the renal/urinary system) are associated with retigabine. Some of them show a dose-response relationship; for some the relation to dose is less clear. None of the CNS effects are unique to retigabine since they are also observed with other AEDs to the same, in a few cases to a higher degree, but in many cases to a lesser degree. Retigabine is associated with weight gain, but this issue is unlikely to be significantly different from the weight gain seen with several other AEDs. Also, a modest QTc prolongation is associated with the 1200 mg/day dose of retigabine.

Discussion on the benefit-risk balance

The efficacy of retigabine has been documented in patients with partial epilepsy in the add-on setting. With the caveat that direct, within-study comparisons have not been conducted, the efficacy at the 900 and 1200 mg/day doses is in the same range as that observed with other AEDs in the add-on setting. Clinically relevant effects were also seen in the subsets of patients who were treated with two or more AEDs, i.e. significantly refractory patients. In line with what is seen with existing AEDs, numerous CNS-related as well as other adverse events are associated with retigabine. Viewed isolated, no single safety and tolerability problem observed with retigabine should in itself preclude marketing authorisation. But the combined evidence suggests that retigabine may belong to the worse end of the spectrum of currently marketed AEDs with respect to safety and tolerability.

However, the benefit-risk balance is considered positive despite the shortcomings mentioned above. There is a significant unmet medical need in epilepsy and treatments for patients not responding adequately to or not tolerating antiepileptic drugs are often shifted to or supplemented with other AEDs based on an individual, patient-by-patient assessment of efficacy, safety and tolerability (as well as other factors). Furthermore, patients are individually titrated to reach a satisfactory balance between seizure control and adverse events. If unacceptable side effects occur, the dose can be lowered or the drug discontinued, and since the vast majority of adverse events will be reversible, permanent harm is unlikely. Thus, retigabine with its novel mechanism of action and documented efficacy in significantly treatment resistant patients could serve as an option – a "building block" – in the armamentarium of AEDs from which the treating physician can choose in order to tailor the optimal antiepileptic treatment for a specific patient.

Retigabine is not a first-line AED, but is considered, in the adjunctive setting, capable of serving a useful purpose as one of several AEDs the neurologist can use to supplement the antiepileptic treatment and find an appropriate balance between seizure control and adverse events.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Trobalt in the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy was favourable and therefore recommended the granting of the marketing authorisation.

1.16. Vibativ

Benefits

- Beneficial effects

New antibacterial agents are required, especially for the treatment of resistant pathogens and the treatment of infections in the increasing number of patients with impaired immune systems.

Telavancin demonstrated comparable efficacy vs. vancomycin in complicated skin and soft tissue infections (cSSTI) and nosocomial pneumonia (NP) studies.

Non-clinical data suggested that telavancin could be active against hetero-resistant vancomycin-insusceptible *S. aureus* (hVISA) and certain vancomycin resistant enterococci (Non-VanA-VRE). However, there are no clinical data to indicate whether telavancin could be effective against such organisms.

- Uncertainty in the knowledge about the beneficial effects.

In some patient sub-groups (e.g. elderly, obese and diabetic patients) the efficacy of telavancin was numerically lower than that observed with vancomycin. The applicant has explored risk factors for clinical failure and documented some instances of imbalances in risk factors between treatment groups but these cannot wholly account for the observations made

Risks

- Unfavourable effects

The clinical data point to an overall conclusion that the safety profile of telavancin is not as good as that of vancomycin. This conclusion applies even after removing patients with pre-existing severe renal impairment from the analyses. There is an imbalance in the mortality rates in the combined HAP/VAP studies in favour of the comparator and there are higher rates of AEs mapping to infections, sepsis and shock in telavancin-treated patients. It is not possible to determine to what extent these imbalances may reflect issues of safety or efficacy or both in individual patients

- Uncertainty in the knowledge about the unfavourable effects

The applicant has explored risk factors for various types of AEs, particularly renal AEs, and documented some instances of imbalances in risk factors between treatment groups but these cannot wholly account for the observations made.

Benefit-risk balance

Notwithstanding a non favourable risk-benefit balance in the overall patient population, it is observed that for subjects with nosocomial pneumonia due to Gram-positive pathogens and who cannot receive commonly-used antibacterial agents (e.g. due to hypersensitivity or due to MRSA) there are limited treatment options for this life-threatening infection. Thus, the risk-benefit balance for telavancin may be considered favourable if its use is confined to carefully specified clinical circumstances and with adequate patient monitoring.

Discussion on the benefit-risk balance

The efficacy of telavancin in both adult target populations (cSSTI and NP) has been shown as comparable to vancomycin.

The apparent increased nephrotoxicity of telavancin as compared to vancomycin remains a major safety concern though. Proposed attempts to restrict the patient population eligible for receipt of telavancin do not wholly resolve these concerns.

However, within the framework of robust risk minimization measures to be in place to support the post-marketing use, telavancin could prove valuable in some instances to treat adult patients affected by nosocomial pneumonia known or suspected to be caused by methicillin-resistant *Staphylococcus aureus.* The target patients would likely be severely ill hospitalised patients under close monitoring, subjected to short-tem treatment. In these carefully specified clinical circumstances, a positive B/R balance for the use of telavancin could be entertained.

In conclusion, the overall benefit/risk balance of telavancin is negative for both of the broad indications initially sought by the applicant.

However, the CHMP considers that the benefit/risk balance of telavancin for the treatment of nosocomial pneumonia known or suspected to be caused by MRSA, exclusively in situations where it is known or suspected that other alternatives are not suitable, is favourable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Vibativ in the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA), exclusively in situations where it is known or suspected that other alternatives are not suitable was favourable and therefore recommended the granting of the marketing authorisation.

1.17. Victrelis

Benefits

- Beneficial effects

The results of both phase III studies show a significant improvement of SVR over standard of care (PEG/RBV), of around 30% in treatment naïve patients (P05216/SPRINT 2) and 40% in treatment experienced patients (P05101/RESPOND 2).

In addition, treatment naïve early responders could benefit from a significant reduction of the total treatment duration (28 weeks as compared to 48 weeks with the current bitherapy)When considering the burden of treatment, this benefit is worthy of being taken into consideration.

Based on these results boceprevir is regarded as representing a significant therapeutic advance that justifies the principle of an accelerated review as decided by the CHMP in November 2010.

Given that SVR is correlated with cure, the addition of boceprevir to the current SOC will significantly increase the individual likelihood of being cured, avoiding progression to cirrhosis and hepatocellular carcinoma.

- Uncertainty in the knowledge about the beneficial effects

Recently the importance of patient genotype IL28B as a strong predictor of SVR in HCV genotype 1 infected patients became known. This was after the start of the phase III studies. Thus patients were not stratified for this baseline characteristic. This information was only available for approximately 60% of treatment naïve and pretreated patients (patients who gave their informed consent).

Although overall addition of BOC to PR resulted in significant higher SVR rates, pharmacogenomic analysis in which SVR rates were evaluated according to patients IL28B genotype, indicate that treatment naïve patients with genotype IL28B CC might not substantially benefit from additional boceprevir to PR, contrary to patients with IL28B genotype CT or TT.

Taking into account the particular burden of anaemia, the applicant is requested to resolve the uncertainties of the added value of boceprevir to the bitherapy in those patients having good predictive factors for interferon responsiveness. This requirement is subject to condition of the marketing authorisation.

ATaking into account that a shortened duration of therapy might not be considered appropriate if this results in a net loss of efficacy, shortened treatment duration has not been found approvable for treatment experienced early responders.

The treatment experienced population in the phase III study, excluded the challenging population of Null Responders qualified as such based on their prior response to pegylated IFN and interferon at week 12. Based on a retrospective analysis performed with requalifying on the basis of their on treatment virologic response at treatment week 4 (using the peginterferon alfa/ribavirin lead in period) as compared to baseline, it was admitted that null responders might gain some benefit in adding Victrelis to the bitherapy. However, this cannot be reliably quantified from the retrospective analysis. Moreover, the optimal management of null responders remains to be established and might in the future require antiviral combination. These considerations are reflected in section 4.4 of the SmPC.

The proportion of patients with cirrhosis is limited, with only 100/1097 (9%) in the phase III in naïve patients and 49/403 (12%) in the phase III in treatment experienced patients. This is reflected in the SmPC.

Risks

- Unfavourable effects

The main safety concern with boceprevir is the increase in the risk of anaemia as compared to bitherapy Forty-nine percent of boceprevir-treated patients experienced anaemia < 10g/dl during treatment versus 29% in placebo-treated subjects.

- Uncertainty in the benefits of the product

One of the main areas of uncertainty is to what extent anaemia associated with the use of boceprevir in combination with standard or care can be managed without EPO, taking into account the need for sufficient ribavirin exposure, and also taking into account that the use of EPO raises safety concerns (risk of PRCA notably) and could impact the benefit risk balance.

Overall even though the data at the time of opinion provide sufficient reassurance, the clinical dossier so far does not allow to fully appreciate to what extent the management of the substantial incremental anaemia induced by boceprevir on top of PR could per se negatively affect the benefit-risk balance of boceprevir, taking into account that ribavirin dose reduction could potentially alter the benefit and on the other hand the EPO could alter the risk.

It is therefore considered compulsory that, in order to establish the most rational management of anaemia, additional investigations be performed by the applicant to better understand the causes (and consequently possible patient characteristics) and potential negative consequences of the management of the high rate of anaemia (as a result of the incremental risk with boceprevir) in patients receiving the tritherapy with boceprevir+ribavirin+peginterferon. To this effect the provision of results of a study comparing EPO versus ribavirin dose reduction as measures of managing anaemia is a condition of the Marketing Authorisation.

The clinical consequence of resistance to boceprevir (in terms of response to boceprevir and impact to subsequent lines of therapies) is unknown and will have to be further substantiated as part of the RMP

Electrophysiological data carries some concerns as regards the cardiotoxicity of the drug in real life (co-administration, electrophysiological disturbances). Attention of physicians is warranted by a specific statement in the SmPC and this issue will be monitored in pharmacovigilance.

Benefit-risk balance

- Benefit-risk balance

Boceprevir has been shown to significantly increase the percentage of treatment naïve and treatment experienced patients chronically infected by HCV genotype 1 achieving Sustained Virologic Response (correlated with cure) and will reduce the treatment duration for some patients.

Considering the limited response rate achieved so far with the Peg-IFN+ ribavirin in patients chronically infected with HCV genotype 1 and given the burden of such a treatment, this represents a significant therapeutic advance.

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This benefit is regarded as overweighing the safety issues associated with this drug, even though the incremental anaemia and perhaps also neutropenia is anticipated as being a particular burden in clinical practice.

For patients with the favourable CC genotype further substantiation of the added benefit of boceprevir to peginterferon alfa and ribavirin is warranted, it is however noted that a higher proportion of patients treated with tritherapy will benefit form a shorter treatment duration as compared to treatment with bitherapy alone.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Victrelis in the treatment of treatment of Chronic Hepatitis C was favourable and therefore recommended the granting of the marketing authorisation subject to

conditions. In line with the current conditions of prescription for the bitherapy with interferon and ribavirin, treatment with Victrelis should be initiated and monitored by a physician experienced in the management of patients with hepatitis C.

1.18. Vyndaqel

Benefits

Beneficial effects

The mode of action of tafamidis was supported by results of the clinical pharmacology and clinical efficacy studies (pivotal study) and is linked to the physiopathology of the disease, i.e. TTR dissociation followed by accumulation of monomers and deposition of amyloid in several tissues. As discussed in the Clinical Pharmacology section, results from Fx-005 on the TTR stabilisation were supportive of justifying the 20 mg once daily tafamidis dosing, i.e. adequate TTR stabilisation. The CHMP also considered that this was further supported by TTR stabilisation data obtained in the long-term extension study Fx-006, as the results were consistent with those seen previously. This TTR stabilisation effect of tafamidis was observed on the wild-type TTR as well as on several TTR mutations including the V30M and non-V30M mutations. In particular, data from study Fx1A-201 indicated that tafamidis was able to stabilize TTR with other mutation than the V30M, as also shown in *in vitro* studies.

As described in the Clinical efficacy section, the pre-specified secondary analyses performed in the evaluable population (PP) on the co-primary endpoints (NIS-LL % of responders and TQoL) and on several secondary endpoints, such as the mean NIS-LL change from baseline to visit at month 18, favoured tafamidis to placebo. In a supplementary multiple imputation analysis, the mean change from baseline in NIS-LL was statistically different between the treatment groups, supporting the previous results. The CHMP considered that the observed effects were clinically relevant.

Of note, tafamidis is the first oral pharmacological treatment proposed in this indication for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment; currently, the only available treatment alternative is the orthotopic liver transplantion.

Uncertainty in the knowledge about the beneficial effects

One pivotal study was conducted in 125 ATTR-PN patients with V30M mutation. The primary objective of this study was to evaluate the effect of tafamidis 20 mg once daily on disease progression over 18 months using two co-primary criteria, i.e. responders on NIS-LL score, defined as patients with a NIS-LL score change from baseline <2 points at month 18, and change from baseline of the TQOL score (Total Norfolk quality of life score).

Applying a conservative approach (patients who underwent liver transplantation before month 18 were withdrawn from the study and were considered as treatment failures), statistically significant results were not obtained at month 18 (primary time point) for either of the two co-primary endpoints; at month 18, 45% of patients in the tafamidis group had an increase in the NIS-LL of <2 as compared to 29.5% patients in the placebo group (p=0.068). TQOL mean (SD) change from baseline to month 18 was 2.4 (14.6) in the tafamidis group as compared to 6.9 (22.9) in the placebo group (p=0.1157).

In this context, the CHMP considered that liver transplantation was scheduled before inclusion in the study and patients on the waiting list for whom an organ became available were allowed to be transplanted for ethical reason. Most of study discontinuations were due to liver transplantation and balanced between groups. When the evaluable population is taken into account, the responder on NIS-LL scores were statistically different between tafamidis and placebo at month 18. A statistically significant difference in favour of the tafamidis group at month 18 was also observed for TQOL.

The description of the transplanted population showed that transplanted patients presented with a more severe disease and longer disease duration than non transplanted patients, but were not differently represented in the two groups. In addition, there were no major differences in the interval to transplantation between tafamidis and placebo group. The efficacy data did not seem to show significant differences between transplanted and non transplanted patients, but the interpretation of these data was considered difficult due to the low number of patients per group. Nevertheless, the CHMP was of the view that transplantation does not seem to be related to the treatment group.

A sensitivity analysis was conducted to impute patients who underwent liver transplantation. The approach used by the applicant was confirmed by supplementary analyses with other imputation methods and was considered supportive, as statistically significant difference for mean NIS-LL change from baseline, favouring tafamidis, was shown.

The CHMP considered that the familial amyloid polyneuropathy is a length-dependent condition with a pre-dominant progressive sensory loss. On the NIS-LL score, the maximum total score possible for the sensory component is 16/88 points compared to the maximum total score possible for the motor component of 64/88. Since the condition manifests predominantly as a sensory neuropathy, the ability of NIS-LL to properly evaluate disease progression in ATTR-PN was considered by the CHMP. In order to provide more data on the clinical relevance of the criteria chosen, i.e NIS-LL and Norfolk, the applicant provided comparison between groups on yearly rate of disease progression, based on a regression model from the cross sectional observational study Fx1A-OS-001 and the data obtained in the Fx-005 study.

The results on annual progression based on both scores as observed in study Fx-005 were consistent with the estimated rate of change from Study Fx1A-OS-001 and supported the utility of the NIS-LL and TQOL in documenting disease progression in ATTR-PN. Thus, the CHMP considered the effects observed on the co-primary parameters clinically relevant.

The CHMP discussed the duration of the pivotal study and the proposed primary time-point (month 18), which was determined empirically. In this context, the CHMP considered that the regression model used to determine the yearly rate of disease progression was valid and was of the view that the study duration can be accepted as sufficient to show an effect in the ATTR-PN patients.

The CHMP also took into consideration results of the open-label studies in ATTR-PN V30M; patients were evaluated by comparing the disease rate of progression in tafamidis treated patients for both NIS-LL and TQOL between the treatment period of each study and the disease rate progression calculated with the placebo arm of the Fx-005 study. These results suggested stability of the disease and maintenance of effect. Nevertheless, the CHMP considered that results of open studies are not as robust as results of controlled studies, that the analyses performed did not follow the multiple imputation technique and that there were uncertainties regarding data handling. However, when comparing the evolution of NIS-LL in tafamidis treated patients during the 18-month double-blind period and the 12-month open-label period, the rate of change in the NIS-LL score was similar for both periods.

The population enrolled in the pivotal study were patients with V30M mutation at an early stage 1 of the disease; the data on patients with non-V30M ATTR-PN patients originated only from a non-

controlled study (Fx1A-201). This study was conducted in 21 patients with non V30M ATTR-PN, which constitutes a population different from the V30M ATTR-PN patients (older patients, more severe disease, more cardiac impairment). These patients were included at late stage 1 of the disease (mean NIS-LL of 27.6 at inclusion). In this context, the CHMP pointed at limitations of comparisons made between different studies (Fx-005 and Fx1A-201) and different patient populations (V30M versus non V30M mutation). However, as the applicant also provided comparison between the monthly rate of change on the NIS score before vs after treatment with tafamidis and the TTR stabilisation data were favourable irrespective of the mutation, the CHMP considered that extrapolation from V30M to non V30M patients was acceptable. The SmPC section 5.1 is phrased accordingly, i.e. addressing the expected beneficial effect in patients with mutations other than V30M.

Risks

Unfavourable effects

Overall, no major safety concerns were identified in the target population treated with tafamidis. The adverse events were generally mild to moderate in severity, mostly represented by urinary tract infection, infections (mainly respiratory infections), diarrhoea, upper abdominal pain, headache, pain in the extremity and vomiting.

Infections (mainly represented by the urinary tract infections) and infestations were the main events reported in the tafamidis group in the pivotal study Fx-005. In this study, the UTIs were observed in 23.1% of patients in tafamidis group versus 12.7% in placebo group. The majority of events was responsive to antibiotics and did not require interruption or discontinuation of the study drug. Given the higher incidence of UTIs in the tafamidis group, a causal relationship between tafamidis and UTI could not be ruled out and the UTIs were considered as an important identified risk by the CHMP.

A higher incidence of vaginal infections in women was observed in tafamidis (18.2%) vs placebo (8.1%) in the pivotal study; all vaginal infections were mild and non-serious and none required study drug interruption or discontinuation. Although the mechanism of this event is not known, vaginal infection is considered as an important identified risk.

Diarrhoea was reported more frequently in patients treated with tafamidis. Among the two cases of diarrhoea which were considered severe, one led to drug discontinuation due to worsening of diarrhoea. The role of tafamidis in this case remained unclear. Despite diarrhoea being typical of ATTR-PN, given the higher incidence of diarrhoea in the tafamidis group, the CHMP concluded that a causal relationship could not be ruled out and diarrhoea was considered as an identified risk.

Conduction and rhythm disorders were thoroughly analyzed by the applicant. Based on the data provided, no increased risk of conduction or rhythm abnormalities associated with the use of tafamidis was identified in the studies.

Uncertainty in the knowledge about the unfavourable effects

Based on one case of liver function test abnormalities, hepatoxicity was considered as an important potential risk. Several possible mechanisms (enzyme induction, metabolism and thyroid hormone disruption) were proposed as underlying the potential hepatotoxicity, but the relationship remains uncertain. Although a negative re-challenge was eventually observed in study Fx1A-303 in the affected patient, this unfavourable effect was taken into account in the context of a limited exposure to tafamidis in the pivotal study (65 patients).

The CHMP considered that data on special populations, such as the elderly and patients with renal impairment are scarce, but considered this in the context of the rare nature of the disorder as acceptable. Only one pregnancy in a patient treated with tafamidis was reported, with no congenital abnormality in the newborn. Due to the limited data on pregnancy, no conclusions on the use of tafamidis could be made and the use of the product during pregnancy was not recommended.

The effect on the thyroid function was also discussed in detail by the CHMP. In the pivotal study Fx-005 no significant changes for thyroid functions were seen from baseline and mean change was similar to placebo treated patients at all time points. The values of thyroid function parameters were also within the normal ranges at baseline and at all time points during study Fx-006. Based on these observations the CHMP considered that the theoretical risk of tafamidis on thyroid function was unlikely, but could not be completely ruled out. In particular, the CHMP was of the opinion that despite absence of relevant effect on the thyroid function, tafamidis treatment may have subtle impact on the thyroid function due to the competition to the binding proteins. In this context, the CHMP was of the opinion, that changes of thyroid function should be considered as an important potential risk in the RMP.

The CHMP noted that in the chromosomal aberration assay in human peripheral lymphocytes, a dose-dependant increase of polyploidy was observed in the presence of S9. Considering the unclear relevance of the finding and the large safety margins regarding micronucleus induction (>70) as well as the safety margin regarding polyploidy in the chromosome aberration assay (=18), the CHMP concluded that in the context of a serious disease with a lack of therapeutic options, this finding did not impact negatively on the benefit-risk balance of tafamidis. One impurity with an unclear genotoxic potential was seen in the study on impurities. Due its negligible levels in the final product, the CHMP was of the opinion that this finding would not impact on the benefit-risk balance, either.

Benefit-risk balance

Importance of favourable and unfavourable effects

Tafamidis is the first oral pharmacological treatment proposed in the treatment of ATTR-PN patients, which is a severe, progressive orphan disease, with a fatal evolution in around 10 years. The mode of action of tafamidis is linked to the pathophysiology of the disease, with a TTR stabilisation effect on several TTR mutations and wild-type TTR. One pivotal double blind placebo controlled study has been conducted in 128 ATTR-PN patients with V30M mutation. This study failed to attain its primary objectives. However, the other pre-specified analyses and results on secondary criteria showed statistically significant differences in favour of tafamidis. Analyses with multiple imputations showed a statistically significant difference in mean change from baseline for the NIS-LL score. The effects observed were considered clinically relevant. Supplementary analyses performed by the applicant, determining the yearly rate of progression of the disease and analyses of efficacy according to different thresholds for responders also allowed to validate the clinical relevance of the effect.

Tafamidis was well tolerated across studies in both healthy volunteers and patients with ATTR-PN. Overall, no major safety concerns were identified in the target population treated with tafamidis. The adverse events were generally mild to moderate in severity. Identification of one case of hepatotoxicity might be of clinical relevance. In this context, the CHMP concluded that hepatotoxicity will be further monitored in the post-authorisation setting by means of routine pharmacovigilance activities including use of data capture aid for hepatotoxicity, collection of data in the ongoing study Fx1A-303 and collection of data on adverse events in the TTR-associated amyloidosis outcomes survey (THAOS). These pharmacovigilance measures were deemed satisfactory by the CHMP to further characterize this potential risk.

The benefit-risk of tafamidis in ATTR-PN patients with non V30M mutation is based on an open label study and the data are therefore not robust. However, the applicant provided a comparison of the monthly rate of change on NIS before and after treatment with tafamidis and the CHMP agreed that this, together with the TTR stabilisation data, is supportive of the extrapolation from V30M to non V30M patients. In order to collect more information on the efficacy and safety of tafamidis in non V30M patients, the CHMP requested that a dedicated sub-study shall be performed by the applicant to further evaluate tafamidis safety in non V30M patients and to collect further clinical data on the patients´ neurologic status.

Discussion on the benefit-risk balance

The pivotal phase II/III study did not show statistically significant differences on the primary analysis, conducted with a conservative approach, i.e., with patients undergoing liver transplantation during the study considered as treatment failures. The other pre-specified and supplementary (with multiple imputations) analyses and results on secondary criteria showed statistically significant differences in favour of tafamidis. Furthermore, other supplementary analyses performed by the applicant, i.e. determination of yearly rate of progression of the disease and analyses of efficacy according to different thresholds for responders allowed to validate the clinical relevance of the effect.

The data on patient exposure showed that 308 individuals received at least one dose of tafamidis, 147 ATTR patients for at least 6 months, 113 for at least 12 months and 43 for at least 2 years. The safety of tafamidis, evaluated in the patients included in the studies and in healthy volunteers, is re-assuring and no strong signal seemed to emerge. The CHMP considered that identified risks will be monitored and are manageable in the post-authorisation setting as described in the Risk Management Plan. The CHMP also took into consideration that data from the THAOS registry with respect to the V30M mutation will be provided on an annual basis by the MAH; this is reflected in the RMP accordingly. In addition, the CHMP considered that treatment with tafamidis should be initiated by and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid polyneuropathy.

With respect to the benefit-risk balance in ATTR-PN patients including those with the rare (non-V30M) mutations, the CHMP pointed out that the clinical data on the rare mutations originated in an open (uncontrolled) setting and were thus not robust. However, at the same time the CHMP considered the data comparing the monthly rate of change on the NIS-LL score before and after treatment re-assuring and agreed that the mechanism of action together with the results of TTR stabilisation data (clinical pharmacology) were supportive of the extrapolation from V30M to non-V30M patients. In their review, the CHMP concluded that the dataset was sufficient to conclude on a positive benefit-risk balance of tafamidis in the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Taking into due consideration the rarity of the disease, the CHMP requested the marketing authorisation to be granted under exceptional circumstances. In particular, the CHMP took into account the fact that due to the rarity of the non-V30M patient population a standard double-blind placebo study is not feasible and that the applicant cannot be expected to provide comprehensive evidence. In this context, the CHMP concluded that the marketing authorisation under exceptional circumstances should be granted subject to a specific obligation to follow non-V30M patients in a proposed sub-study of the THAOS registry:

Specific obligation:

"Within the planned post-authorisation sub-study of the THAOS registry the MAH shall evaluate in non-V30M patients the effects of Vyndaqel on disease progression and its long term safety as detailed in a

CHMP agreed protocol, and shall provide yearly updates on the collected data within the annual re-assessment."

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by concensus that the risk-benefit balance of Vyndaqel in the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment is favourable and therefore recommends the granting of the marketing authorisation.

1.19. Yellox

Benefits

- Beneficial effects

Two pivotal clinical studies conducted after the same protocol, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, contributed to efficacy data to the sought indication. Those studies were randomised multi-centre, double-masked, parallel studies, investigating the efficacy and safety of topical Bromfenac ophthalmic solution 0.1 % versus placebo, for treatment of ocular inflammation following cataract surgery.

Patients were subjects scheduled for unilateral cataract surgery with posterior chamber intraocular lens implantation. A summed score of ≥ 3 for anterior chamber cells (scale 0-4) and flare (scale 0-4) at the baseline examination (visit 1, study day 1) was required. The therapy was scheduled for up to 14 days The primary endpoint was the proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit 4 (day 15).

The results of those two pivotal studies showed superior efficacy to placebo, in patients with anterior ocular inflammation subsequent to cataract extraction.

- Uncertainty in the knowledge about the beneficial effects.

Two major GCP issues were observed during the review of the pivotal trials: 1) Inadequate blinding of study medication; and 2) Inappropriate data management procedures.

With regards to the impact of the lack of a strict double-masked trial conduct, it is considered unlikely that a bias favouring Yellox would have changed the results of the primary endpoint (and secondary endpoints based on cell and flare scores) to a significant extent. Further, it is considered unlikely that possible unblinding could have favoured Yellox with regard to adverse event reporting.

The concerns pertaining to the GCP issues with non-compliance to the main principles for data management in clinical trials for traceability of source data during the procedures of data verification of the data source have been sufficiently addressed. There were no indications that the deficiencies observed significantly influenced the study results.

There was insufficient information to conclude on whether the efficacy data with the originally sought formulation, BFSS-OS could be extrapolated to Yellox since the small tolerability trial in healthy subjects was not considered useful to bridge the efficacy results obtained in the two pivotal trials, and the rabbit pharmacokinetic study (CRO 28) comparing the ocular penetration of the old formulation

and Yellox lacked assay sensitivity. However, the formulation has been amended and these concerns are no longer considered valid.

It was discussed that the large window, i.e. 16-32 hours, between the surgical procedure and the first application of trial medication may not be optimal in a clinical setting. Post-hoc analyses revealed, however, similar efficacy independent on the time from surgery to first application of the medication. Initiation of therapy prior to surgery may have a beneficial effect in the prevention/treatment of inflammation, but this was not investigated.

Overall, the claimed therapeutic indication "pain" was not supported by the provided data. Since this part of the sought therapeutic indication has been deleted, the problem was considered solved.

Risks

- Unfavourable effects

The reported adverse events pattern is not concerning, either as regards the frequency or the nature of ocular adverse events. A significant post-marketing experience with an estimate of over 20 million exposed patients was reassuring.

A main concern with topical, ocular NSAIDs is the potential risk for adverse effect on the cornea, especially in cases where the treatment duration is prolonged or if the cornea is compromised. This risk is relevant also for Yellox as there are post-marketing reports of such complications including extremely rare, but potentially sight-threatening cases of corneal ulcers and perforations. The same risk is evident in case of off-label use, for example after corneal refractive procedures, or if used long-term in other ocular inflammatory conditions like blepharitis and anterior uveitis.

- Uncertainty in the knowledge about the unfavourable effects

Including the Japanese population, more than 1200 subjects were exposed to bromfenac eye drops during the development programme. However, the quality of the Japanese data might be questioned due to presumed differences in traditions in collection of safety data.

Although most Japanese studies contained a representative patient population, surprisingly few adverse events were reported from these studies and there are uncertainties regarding the quality of reporting and whether this will affect the overall adverse event profile of Yellox.

The exact duration of treatment in some Japanese studies was not identifiable in the dossier - the intended treatment duration was 2 weeks in the phase II studies and in the pivotal trials, but a considerable, though not identifiable, part of the study population received longer therapy. With these uncertainties, the total exposure is rather limited.

Approximately one third of the BFSS-treated population still had signs of a post-operative inflammation after 14 days treatment and it cannot be excluded that Yellox will be used for more than 2 weeks in this subpopulation. Since the experience from longer-term treatment is limited, the magnitude of the risk for corneal complications in case of extended use is not characterised. However, with the SmPC text in section 4.2: "The treatment should not exceed 2 weeks as safety data beyond this is not available", this has been addressed satisfactorily.

Bromfenac was originally approved in the US as an oral formulation for short-term analgesia, but withdrawn from the market due to hepatotoxicity associated with long-term use. No relevant abnormalities in hepatic enzymes were identified in the studied population and there have been no such related post-marketing reports.

Benefit-risk balance

- Importance of favourable and unfavourable effects
    - Clinical context

Presumingly, it would have been in the best interest of the patients to start therapy before surgery, or at least as early as possible after surgery. However, such recommendations are not supported by the study data. The wording in section 4.2 of the SmPC "The dose is one drop of Yellox in the affected eye(s) twice daily, beginning the next day after cataract surgery and continuing through the first 2 weeks of the postoperative period" is in accordance with the pivotal clinical studies.

- Benefit-risk balance

The two pivotal trials showed superior efficacy to vehicle in patients with anterior ocular inflammation subsequent to cataract extraction. The safety and tolerability pattern does not raise major concerns, neither the frequency nor the nature of ocular adverse events. A reassuring and significant post-marketing experience with an estimate of over 20 million exposed patients adds to a positive picture. Systemic or serious adverse events are not a prominent issue. However, the limited experience with a treatment exposure exceeding 2 weeks is a clear limitation.

Discussion on the benefit-risk balance

Overall, the benefits encompassing superior efficacy towards placebo in the treatment of postoperative ocular inflammation following cataract extraction in adults are considered to outweigh the risks.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the benefit-risk balance of Yellox in the treatment of postoperative ocular inflammation following cataract extraction in adults was favourable and therefore recommended the granting of the marketing authorisation.

1.20. Yervoy

Benefits

- Beneficial effects

In the pivotal study MDX010-20, the efficacy of ipilimumab monotherapy and ipilimumab in combination with gp100, in comparison with gp100 monotherapy was investigated.

For ipilimumab monotherapy a median OS of 10.1 months (95% CI; 8.02-13.80) was reported whereas the OS for gp100 monotherapy was only 6.4 months (95% CI; 5.49-8.71). The median OS for ipilimumab plus gp100 was 10.0 months.

Long-term survival data indicates that 54 of the 403 patients in the ipilimumab plus gp100 group, 24 of the 137 patients in the ipilimumab monotherapy group, and 16 of the 136 patients in the gp100 monotherapy group, remain alive for a minimum of 2 years.

The observed OS benefit was consistent within most of the subgroups of patients analysed by the Applicant.

Also in the CA184024 study an OS benefit for patients treated with ipilimumab (DTIC+ipilimumab) was seen in comparison to patients treated with DTIC alone. The CHMP acknowledged the results of CA184024 as supportive for the efficacy results obtained in the MDX010-20 study.

- Uncertainty in the knowledge about the beneficial effects.

For women above 50 years of age, the data supporting an OS benefit of YERVOY treatment were limited: A HR close to 1 for this patient group was observed in MDX010-20 study and just above 1 in Study CA184024. As the subgroup analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data. The efficacy and safety of ipilimumab in these patients will continue to be analysed in ongoing and future clinical trials, particularly in the dose comparison study to be conducted.

The number of patients with active brain metastases treated with ipilimumab is limited. Moreover, no efficacy data for patients with ocular melanoma are available.

In vitro data indicated that ipilimumab does not elicit CDC up to concentrations of 50 µg/ml. However, this is lower than the concentrations reached in human plasma after the 3mg/kg dose (Cmax ~85 µg/ml). The results of nonclinical pharmacodynamic studies indicated that the dose of 10 mg/kg is certainly an active level, but no dose-response was studied, and the dose inducing the maximum pharmacological effect is not known. Efficacy of the 3 mg/kg dose has been demonstrated in the pivotal study MDX010-20. Results of phase II studies suggest that a better efficacy might be expected for the 10 mg/kg dose, but also a higher toxicity is envisaged. However, results from the pivotal study with 3 mg/kg dose cannot be directly compared to those obtained from supportive studies conducted using the 10 mg/kg dose. A randomised comparison of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint is warranted.

Risks

- Unfavourable effects

The suggested working mechanism of ipilimumab is that by blocking CTLA-4, ipilimumab potentiates T-cell activation and proliferation. It has been hypothesised that an increased immune activity indirectly impact the tumour cells, however the increased activity of the immune system also contributes to the appearances of immune related AEs .

Throughout the clinical program in advanced melanoma, the vast majority (>96%) of patients with metastatic melanoma experienced AE of any grade during the induction phase, including in the gp100 monotherapy group as well as all ipilimumab treatment groups. Most common safety events of any grade reported in patients receiving ipilimumab were those affecting the GI tract and skin. These AEs are classified as irAEs and include diarrhoea, pruritus and rash, each were more commonly reported in the ipilimumab groups than in the gp100 group. In addition, the incidences of colitis and endocrine insufficiency were higher in the ipilimumab groups compared to the incidence in the gp100 group.

Diarrhoea and colitis were consistently the most common treatment-related SAEs reported in the clinical database for patients receiving ipilimumab across studies and doses.

In the MDX010-20 study, treatment-related SAEs were reported in 16.8%, 12.6% and 3.8% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100 and gp100 monotherapy groups, respectively.

Treatment-related death was reported for all treatment groups in the MDX010-20 study. Treatment-related deaths (for the entire study duration) were reported in 3.1%, 2.1%, and 1.5% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively.

No treatment related deaths were reported in the CA184024 study. The percentage of treatment related death is about 2% in the submitted phase 2 study.

In MDX010-20, treatment-related AEs leading to discontinuation of study therapy were reported in 9.9%, 6.8%, and 3.0% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively. Treatment-related adverse events leading to discontinuation were reported in 33.6% for the CA184024 study.

The safety results of the CA184024 confirm the safety issues indentified in the MDX010-20 study. he characteristics of irAEs reported for the CA184024 study are reasonably similar to the safety issues identified in the MDX010-20 study.

Extensive guidance for the management of irAE including the use of systemic corticosteroids is included in the product information. The development or maintenance of clinical activity following ipilimumab treatment was similar with or without the use of systemic corticosteroids.

- Uncertainty in the knowledge about the unfavourable effects

No efficacy and safety data for patients with a history of any autoimmune disease other than vitiligo or adequately controlled endocrine deficiencies are available from the submitted clinical studies. Considering the supposed mechanism of action and the observed AEs which were mainly immune related, additional safety concerns might be expected in these patients. Therefore, a warning has been included that ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening and used with caution in other patients with a history of autoimmune disease, after careful consideration of the potential risk-benefit on an individual basis. This population that was not studied has been included in the risk management plan and further data should continue to be collected.

Benefit-risk balance

- Importance of favourable and unfavourable effects

An improvement of overall survival was reported in the pivotal study in adult patients with advanced previously treated melanoma receiving ipilimumab monotherapy. Overall survival is an important objective in this population because of the very short long-term prognosis.

In patients who received 3 mg/kg YERVOY monotherapy in MDX010-20, the most frequently reported adverse reactions (≥ 10% of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority were mild to moderate (Grade 1 or 2).

- Benefit-risk balance

Extensive guidance for the management of irAEs including the use of systemic corticosteroids has been included in the product information.

The CHMP considered that efficacy of 3 mg/kg ipilimumab treatment for patients with previously treated advanced melanoma patients, was demonstrated. The OS benefit is clinically relevant and compensates for the irAEs found.

The severity and the number reported AEs constitute a need for an ongoing (post approval) search for sub-groups of patients for whom ipilimumab treatment will appear to work out more favourably, and for those in which it is less beneficial (possibly women above 50 years of age, patients with primary CNS or ocular melanoma). This is in particular important for sub-groups who are especially at risk to experience (severe) AEs, for instance patients with autoimmune disease.

While the benefit-risk balance associated with the 3 mg/kg ipilimumab dosing is considered clearly positive, to gain a better understanding of the effect of dose of ipilimumab and benefits and risks, a further randomised study comparing of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint is considered necessary.

Discussion on the benefit-risk balance

The overall quality of the drug product has been demonstrated. The product is controlled by adequate test methods and specifications. Although the testing of clearance of host cell proteins (HCP) is sufficiently controlled by a generic CHO HCP assay, this generic assay is not considered the most suitable for its purpose based on the difficulties to fully demonstrate its sensitivity and accuracy. With this respect, the applicant is asked to continue the development and validation of a process-specific HCP assay.

The efficacy of ipilimumab in the treatment of advanced melanoma has been shown. Because a clinical relevant OS benefit is observed, the CHMP was of the opinion that the overall risk/benefit balance of Yervoy is positive for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Yervoy in the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy was favourable and therefore recommended the granting of the marketing authorisation.

1.21. Zytiga

Benefits

Beneficial effects

One pivotal trial was submitted in support of the efficacy of abiraterone acetate in combination with concomitant low dose glucocorticoid therapy in patients with advanced metastatic castrate refractory prostate cancer (mCRPC) in a population that had previously failed to 1 or 2 docetaxel-based regimens. Median overall survival was 14.8 months in the abiraterone group and 10.9 months in the placebo group. There was a 33% relative improvement in 12-month survival rate (60% in the abiraterone acetate group versus 45% in the placebo group). The study met therefore its primary endpoint at the pre-specified significance level (0.0141) required to cross the efficacy boundary for the interim analysis at the clinical cut-off (22 January 2010). Treatment with abiraterone acetate decreased the risk of death by 35% compared with placebo (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). The benefit in survival was confirmed in an updated analysis (cutoff of 20 September 2010, HR=0.740; 95%CI: 0.638, 0.859; p<0.0001), showing a median survival of 15.8 months for the AA group versus 11.2 months for the placebo group. Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favourable across all subgroups (ECOG, pain score, prior lines of chemotherapy, type of progression, age, visceral disease, baseline PSA, LDH or alkaline phosphatase, and geographical region).

This effect was further substantiated by results in the pre-specified secondary efficacy endpoints: time to biochemical or radiological disease progression was significantly increased, such as time to PSA progression [10.2 months versus 6.6 months in controls, HR=0.58, p<0.0001] or radiographic progression-free survival [5.6 months versus 3.6 months in controls, HR=0.673, p<0.0001]. PSA response rate was significantly greater in abiraterone treated patients compared to the placebo group (38% versus 10%, p<0.0001), also when only confirmed PSA responses were considered (29% versus 6%, p<0.0001), as was objective response rate in the subset of patients with baseline measurable disease (14% versus 3%, p<0.0001). Finally, symptom-related endpoints, such as pain palliation, time to pain progression, skeletal-related events, and quality of life scores also tended to favour abiraterone-treated patients over placebo-control ones.

Uncertainty in the knowledge about the beneficial effects

One limitation is the limited number of non-Caucasian patients in the pivotal clinical trial. Moreover, patients having received prior ketoconazol therapy were excluded from the study. Both issues are considered relevant information for prescribers which was reflected in the SmPC. Moreover, the lack of data in non-white patients is important missing information reflected in the RMP.

Risks

Unfavourable effects

The most frequently reported AEs reported in the pivotal trial were fatigue (44% and 43% in the abiraterone acetate and placebo groups, respectively), back pain (30% and 33%, respectively), nausea (30% and 32%, respectively), and constipation (26% and 31%, respectively), consistent with the natural history of mCRPC. In the overall abiraterone acetate group, the most frequently reported AEs were fatigue (44%), nausea (28%), back pain (27%), and arthralgia and edema peripheral (26%).

The most common adverse drug reactions observed in the overall abiraterone acetate group (n=1,070) were peripheral edema, hypokalemia, urinary tract infection, and hypertension. Consistent with the pharmacologic mechanism of action of abiraterone, mineralocorticoid-related toxicities (based on the SMQ grouping) such as fluid retention/edema (31% versus 22%), hypokalemia (17% versus 8%), and hypertension (10% versus 8%) were observed more frequently for patients treated with abiraterone acetate. Co-administration of prednisone from the beginning of treatment and frequent electrolyte monitoring in Study COU-AA-301 appeared to decrease the incidence and severity of the AEs related to mineralocorticoid excess compared with some of the early stage studies which did not include the uniform administration of low-dose glucocorticosteroids. Most of these events were Grade 1 or 2, non-SAEs (1% or less for each term, respectively), and infrequently interfered with abiraterone acetate treatment, as evidenced by low rates of dose modifications/reductions, treatment discontinuations or deaths due to any of the 3 terms (1% or less for each term, respectively).

In addition to the expected AEs due to increased mineralocorticoid activity, the following key safety risks have been identified:

The incidence of cardiac events was slightly higher in the abiraterone acetate and prednisone group with no differences in the rates of cardiac-related death (<1% of patients in each group).

There is a risk for increased urinary infections.

Finally, there was an increase for hepatotoxic events in relation to treatment with abiraterone (10% vs 8% in AA and placebo, respectively). Increments in hepatic enzymes occurring during treatment were managed with careful laboratory monitoring, treatment interruptions and retreatment only after return

of the LFTs to baseline or Grade 1. Although no patients treated with abiraterone acetate were identified as having met all Hy's Law criteria, 2 cases of drug-induced liver injury were identified; 1 in the pivotal study and 1 in the early stage study, COU-AA-003. Hepatotoxicity is considered an identified risk for abiraterone therapy.

Uncertainty in the knowledge about the unfavourable effects

Overall the unfavourable effects were predictable and in keeping with the mechanism of action of abiraterone (mineralocorticoid excess) or the nature of the disease. However, the role of abiraterone in hepatotoxicity is not fully understood. Increases in hepatic enzymes were observed during treatment with abiraterone and 2 patients (1 patient in the pivotal Study COU-AA-301 and 1 patient in Phase 2 Study COU-AA-003) were identified as potentially having met Hy's Law criteria. Routine and additional pharmacovigilance activities (see Table 27 above) are expected to provide further insight into the role of abiraterone in hepatotoxicity.

The potential risk for drug-drug interactions is not fully elucidated. In particular, the possible effect of CYP3A4 inducers leading to a possible decrease of effect of abiraterone due to enhanced elimination is possible. Ongoing interaction studies with inducers and inhibitors of CYP3A4 will elucidate the effect of CYP3A4 inhibition and especially of CYP3A4 induction on the pharmacokinetics of abiraterone.

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with abiraterone showed an improvement in the median overall survival in a population with very few therapeutic alternatives. Results in key secondary endpoints supported the observed improvement in overall survival and measures of functional status and symptom-related endpoints also tended to favour abiraterone-treated patients over placebo-control ones. Abiraterone showed a clear antitumour effect in patients with advanced mCRPC that have failed prior docetaxel therapy. The results are considered to be mature, robust, consistent, and of clinical relevance.

The safety profile is considered acceptable and generally manageable with basic medical interventions (oral potassium supplements, diuretics and antihypertensive medication). Toxicities were generally mild, and resulted in infrequent discontinuations. In this regard it should be noted that the safety profile of abiraterone acetate is distinct from that typically induced by conventional cytotoxic agents, frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, or life-threatening. Indeed, AEs such as hypertension or hypokalemia are generally asymptomatic, and although fluid retention/edema or urinary tract infections may be more disturbing to the patient, abiraterone does not induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia, alopecia, etc, which may not only be associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life, which is particularly relevant in the context of non-curative therapy for an end-stage disease.

Benefit-risk balance

Overall, the efficacy of abiraterone has been demonstrated. The fact that this is an orally administered medicine is considered an additional advantage for this clinical setting. The adverse event profile is expected according to the mechanism of action of abiraterone and generally manageable with basic medical interventions.

Discussion on the benefit-risk balance

The benefit-risk balance for abiraterone in combination with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients whose disease has progressed on or after a docetaxel-based chemotherapy regimen is considered positive. The favourable effects outweigh the negative effects and Zytiga is expected to be of major public health interest due to the poor prognosis of the target population that represents a high unmet medical need, while the novel mechanism of abiraterone may offer an alternative therapeutic option for this patient population.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zytiga in combination prednisone or prednisolone in the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen is favourable and therefore recommends the granting of the marketing authorisation.

2. Benefit Risk assessments - from the EPAR of New active substance (NAS) applications with unfavourable CHMP outcomes in 2011 (as available on 01 February 2012)

2.1. Beprana

The company withdrew the application before the final CHMP opinion. The following information has been published on the EMA website: "Based on the review of the data and the company's response to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Beprana could not have been approved for the relief of signs and symptoms of osteoarthritis of the knee and hip.

The CHMP noted that while there was evidence showing that Beprana was effective in relieving the signs and symptoms of osteoarthritis of the knee and hip, its benefits were not sufficient to outweigh the identified risks. The Committee had concerns about its effect on blood pressure and the potential risk of toxic effects in the liver."

2.2. Joicela

The company withdrew the application before the final CHMP opinion. The following information has been published on the EMA website: "Based on the review of the data and the company's response to the CHMP's lists of questions, the CHMP had some concerns and was of the provisional opinion that Joicela could not have been approved for the symptomatic treatment of osteoarthritis (swelling and pain in the joints) of the knee and hip in adults who are not carriers of DQA1*0102.

At the time of the withdrawal, the CHMP was of the view that the benefits of Joicela did not outweigh its risks, particularly its risk of liver toxicity. The Committee was not convinced that screening patients for the DQA1*0102 gene variant sufficiently reduced this risk."

2.3. Kalbitor

The company withdrew the application before the final CHMP opinion. The following information has been published on the EMA website: "Based on the review of the data and the company's response to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Kalbitor could not have been approved.

The CHMP had concerns about hypersensitivity reactions, which were seen at a higher rate in patients treated with Kalbitor. Hypersensitivity reactions occur when the body's immune system reacts against a medicine, and include reactions commonly known as allergic reactions. The CHMP also had concerns related to the effectiveness of the proposed doses in heavier patients.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Kalbitor did not outweigh its risks."

2.4. Luveniq

The company withdrew the application prior to the final CHMP Opinion after appeal following an initial negative CHMP Opinion. The following information has been published on the EMA website: "Based on the review of the data, at the time of the withdrawal, the CHMP had previously given a negative opinion in June 2011 recommending that the marketing authorisation be refused for Luveniq for the

treatment of chronic active non-infectious uveitis involving the intermediate or posterior segments of the eye.

At the time of the negative opinion, the CHMP was not convinced that the benefits of Luveniq had been shown to outweigh the risks as a treatment for chronic non-infectious uveitis. Only one main study supported the application and the results did not show in a robust way that Luveniq was more effective than placebo at reducing eye inflammation, while no difference was seen in the patients' eyesight compared with placebo. Luveniq also caused side effects which are known to occur with this type of immunosuppressive medicine, including hypertension (high blood pressure). Therefore, the CHMP was of the opinion that the benefits of Luveniq had not been shown to outweigh its risks and recommended that it be refused marketing authorisation."

2.5. Ozespa

The company withdrew the application prior to receipt of the CHMP list of question. As the CHMP was evaluating the initial documentation provided by the company, it had not yet made any recommendations.

2.6. Tekinex

The company withdrew the application before the final CHMP opinion. The following information has been published on the EMA website: "Based on the review of the data, at the time of the withdrawal the CHMP had some concerns and was of the provisional opinion that Tekinex could not have been approved.

The CHMP was of the view that the medicine's benefits were uncertain. There was also insufficient follow-up of the patients following treatment and the Committee was doubtful about the medicine being safe enough to be self-administered by patients as intended by the company. The CHMP also had concerns about the doses used in the study and the criteria used for measuring the medicine's effectiveness. Finally, following an inspection of the study sites, the Committee noted that there were some inconsistencies in the application that could have affected the reliability of the study results.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Tekinex did not outweigh its risks."

3. Benefit Risk assessments - from the EPAR of extensions of indications with positive CHMP outcomes in 2011 (as available on 01 February 2012)

3.1. Afinitor

Benefits

- Beneficial effects

The primary objective of the pivotal study C2324 was increase in PFS in everolimus-treated patients compared to placebo plus BSC-treated patients. Based on study C2324, there was a median PFS of 11.04 vs 4.60 months per INV for everolimus and placebo, respectively (HR 0.35, 95%CI 0.27-0.45; p<0.001). These results were consistent with the PFS results from the IAC and IRC.

- Uncertainty in the knowledge about the beneficial effects.

No advantage in OS or time to deterioration of the WHO performance were observed. Because of the cross-over design of the pivotal study, analysis of the secondary endpoints overall survival and WHO performance status was impaired. It is uncertain whether the improvement in PFS would translate into a long term beneficial effect in terms of OS. However, the effect observed in terms of PFS was considered clinically relevant and convincing even in the absence of an effect in terms of OS.

Concerning study C2325 which included patients with carcinoid tumours, the CHMP found this study problematic as PFS only reached statistical significance in a supportive analysis (INV) and not in the primary analysis (IAC) and more deaths (100 vs. 85 total) were reported from the everolimus treatment group (HR 1.22; 95%CI: 0.91-1.62; p=0.908). Therefore, the CHMP did not support the extension of the indication in advanced pancreatic NET in carcinoid tumours.

Risks

- Unfavourable effects

The most common ADRs, with an incidence ≥ 10% in the pooled dataset, were stomatitis, rash, diarrhea, fatigue, nausea, decreased appetite, dysgeusia, anemia, weight decreased, peripheral edema, headache, aphthous stomatitis, hyperglycemia, asthenia, vomiting, pruritus, thrombocytopenia, and epistaxis.

The most common grade 3-4 ADRs, with an incidence of ≥ 2%, were hyperglycemia, stomatitis, diarrhea, fatigue, thrombocytopenia, anemia, neutropenia, hypophosphatemia, and asthenia.

The most frequently reported SAEs were abdominal pain, pyrexia and pneumonia.

The safety of everolimus was largely consistent with observations from previous everolimus studies in an oncology setting, though the CHMP noted that ADRs occured in higher frequencies which was likely attributed to the 2-fold increase in patient exposure to everolimus compared to that of the placebo group. Adverse events were predictable, largely low-grade, manageable, reversible and non-cumulative.

The number of on-treatment deaths for study C2324 was higher with everolimus treatment: 7 patients (3.4 %) and 1 (0.5 %) with everolimus vs. placebo, respectively. Seven deaths were reported as related to AEs, of these one death was considered as related, and for 6 cases a possible relation could not be ruled out.

During the open-label phases of studies C2324 and C2325, 9 deaths with suspected causality to AEs occurred with a similar AE profile. In study C2239 4 AE-related deaths occurred which were of the respiratory or infections' SOC.

- Uncertainty in the knowledge about the unfavourable effects

The concomitant administration of somatostatin analogues (e.g. octreotide) increased the frequency of reported ADRs in patients with carcinoid tumours. It was unclear to what extent add-on to octreotide contributed to the poor tolerability. However, the analysis of the concentrations of octreotide and everolimus showed no effect on the withdrawal of carcinoid patients due to AEs suggesting a lack of influence of octreotide on the withdrawal of patients due to AEs. Data from the pNET study where octreotide co-medication was an option at the discretion of the investigator showed no increase in toxicity when both treatments were combined.

Benefit-risk balance

- Importance of favourable and unfavourable effects

PFS was considered an important and appropriate primary endpoint for the study C2324 in pancreatic neuroendocrine tumours. The HR and increase in median PFS were statistically significant. The cross-over design confounded the data for overall survival, thus the effect on overall survival could not be ascertained. However, the treatment effect in terms of PFS was considered clinically relevant and convincing even in the absence of an effect in terms of OS for this patient population, as few approved pharmacological treatment options are available.

Long term data on the patient population were not available. The safety of everolimus was largely consistent with observations from previous everolimus studies. The identified ADRs were mostly well tolerated and graded as mild and manageable.

- Benefit-risk balance

Although the increase in PFS in study C2324 was not supported with additional endpoints, the effect still remained clinically relevant. The adverse events reported were considered acceptable for a patient population of adult patients with advanced neuroendocrine tumours of pancreatic origin. Thus, it was considered that the clinical benefit observed with the improvement of PFS outweighed the risks previously identified in the safety population.

3.2. Alimta

Benefits

- Beneficial effects

The present application for extension of the existing Alimta maintenance indication after first line treatment of NSCLC is mainly based on the PARAMOUNT pivotal study, which is a multicentre, randomised, double-blind, placebo-controlled phase III study designed to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC in terms of objective PFS time in patients with Stage IIIB or Stage IV non-squamous NSCLC whose disease has not progressed during 4 cycles of pemetrexed and cisplatin induction chemotherapy.

This trial met its primary objective, as the analysis showed a statistically significant (log rank p=.00006) increase in investigator-assessed PFS for patients treated with maintenance pemetrexed.

The HR was 0.62 (95% CI: 0.49 to 0.79; Wald's p=.00007) which represents a 38% reduction in the risk of disease progression for patients receiving pemetrexed. Independently assessed median PFS following induction therapy was 3.94 months in the pemetrexed arm and 2.6 months in the placebo arm. The treatment effect was statistically significant (HR = 0.64; 95% CI: 0.51 to 0.81; Wald's p =.00025).

A clear difference in PFS could be observed from the second month of treatment. This difference remained in favour of the pemetrexed arm up to 11 months. Although results are consistent in subgroups, there are some subgroups for which the 95% CI of HR includes 1, hence no difference could be confirmed statistically (see figure 3). However, few PFS events had occurred in these subgroups thus leading to wide 95% CIs.

Secondary efficacy results showed that the tumour response rate of the maintenance therapy (CR + PR) was 4.2% in the pemetrexed arm and 1.1% in the placebo arm (p=.067).

Results of the first preliminary survival analysis showed a preliminary improvement of the median of 1.57 months. Survival was immature with high censoring rates (78.6% and 74.4% for the pemetrexed and placebo arms, respectively). For a second preliminary analysis of OS results, 299 events had occurred with censoring rates of 48% and 38% in the pemetrexed and placebo arms, respectively. The hazard ratio was 0.78 (95% CI: 0.61 to 0.98; log rank p= 0.034). The median OS benefit for patients receiving pemetrexed was 2.76 months.

- Uncertainty in the knowledge about the beneficial effects

There are no significant uncertainties in the knowledge of the beneficial effects.

Risks

- Unfavourable effects

Fifty six (56) deaths occurred during induction treatment of which 11 were due to study drug-related AEs. Among the 15 death due to unrelated AEs, 4 were secondary to pulmonary embolism. Comparison of data from the PARAMOUNT and JMDB studies showed a higher toxicity during JMDB. Increased toxicity could be explained by a higher exposure to pemetrexed-cisplatin (up to 6 cycles) in comparison to PARAMOUNT induction treatment (4 cycles). However, no new safety signal emerged from the comparison of the PARAMOUNT induction treatment and JMDB. Overall, the safety results observed in the PARAMOUNT study are consistent with the known safety profile of pemetrexed.

During maintenance treatment, there was no difference between placebo and pemetrexed arms in term of deaths. As expected more patients in the pemetrexed arm had dose delays due to adverse events (20.1%) in comparison to the placebo arm (14.4%). The most common reasons for dose delays in active arm were AEs related to hematotoxicity (anaemia, neutropenia, leukopenia, haemoglobin decreased). Similarly dose reductions were more frequent in pemetrexed arm (3.1%) in comparison to the placebo arm (0.6%). All the dose reductions were due to AEs.

During maintenance treatment, frequencies of SAEs and related SAEs were higher in the pemetrexed arm. However, due to the small number of SAEs, the difference between both arms was non-significant. Overall, 14 patients (3.9%) in the pemetrexed arm and 3 (1.7%) in the placebo arm, discontinued treatment due to SAEs.

- Uncertainty in the knowledge about the unfavourable effects

Pulmonary embolism is a newly identified Adverse Drug Reaction (ADR) for pemetrexed. As such, it was included in section 4.8 of the SmPC and it will be included in the next version of the RMP which the MAH proposes to submit in early 2012.

Benefit-risk balance

- Importance of favourable and unfavourable effects

The gain in median PFS of 1.38 months was highly statistically significant. Based on preliminary analyses, a statistically significant difference in OS has not been shown, but the preliminary difference in median OS of 2.76 months suggests that at least a detrimental effect is unlikely.

- Benefit-risk balance

The benefit-risk balance of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination is considered as positive, as the demonstrated statistically significant gain in PFS outweighs the added toxicity of pemetrexed given as maintenance treatment after induction chemotherapy with a platinum-pemetrexed combination.

Discussion on the benefit-risk balance

The PARAMOUNT study added a new piece of information on the use of pemetrexed as maintenance treatment of NSCLC other than predominantly squamous cell histology after first line induction treatment with platinum chemotherapy that included pemetrexed. Two questions resulting from the pemetrexed maintenance treatment had been: 1) whether the OS benefit observed in trial JMEN was only due to the delayed administration of otherwise efficacious pemetrexed and 2) whether pemetrexed maintenance is beneficial (even) after pemetrexed induction. PARAMOUNT showed that patients derive additional benefit from continuing pemetrexed as maintenance treatment after induction chemotherapy which includes pemetrexed.

Based on PARAMOUNT and earlier studies in both maintenance (JMEN) and first-line (JMDB) treatment, there is little uncertainty in the knowledge of favourable and unfavourable effects in the use of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination to change the benefit-risk balance.

3.3. Avastin (ovarian cancer)

Benefits

- Beneficial effects

Both pivotal studies of bevacizumab in combination with carboplatin and paclitaxel in the front-line treatment of ovarian cancer (study GOG-0218 and study BO17707) showed a statistically significant increase in PFS in patients receiving bevacizumab in combination with chemotherapy followed by extended bevacizumab compared to patients in the control arms. The absolute difference in PFS was between 2-4 months and the reduction in risk of progression or death was about 30%.Furthermore, the observed PFS benefit (4.1 months) in study GOG-218 has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

No detrimental effect was shown for OS in any of the studies. Nevertheless, further follow-up is needed to further clarify the benefit-risk of the product and the MAH is requested to provide this analysis by 31/03/2012 for study GOG-0218 and by 31/12/2013 for study BO17707 (see Annex II of the PI).

There were no detrimental effects on quality of life according to the results on patient reported outcomes.

- Uncertainty in the knowledge about the beneficial effects.

There were uncertainties regarding the limited evidence of a clinically relevant benefit at an acceptable toxicity level for patients with early high risk stages of EOC at the proposed dosage. Therefore this patient population has been excluded from the indication and the updated applied indication includes patients with advanced (FIGO stages III B, III C and IV) ovarian cancer. The recommendation on dose and duration of treatment for patients with advanced disease remained the same.

Risks

- Unfavourable effects

Overall, the review of AEs in the light of bevacizumab known safety profile did not reveal any unexpected findings. Safety results and adverse drug reactions encountered with the combination of carboplatin, paclitaxel and bevacizumab from pivotal studies GOG-0218 and BO17707 are as it can be expected from the present knowledge of the safety profile of the three drugs. No new safety concerns have been identified.

The most common adverse events observed were gastrointestinal disorders (83-87% across treatment arms), general disorders (fatigue), musculoskeletal disorders (myalgia/ arthralgia), nervous disorders (peripheral neuropathy) and skin and subcutaneous disorders (alopecia). Of note, common adverse events associated with carboplatin are myelosuppression (particularly thrombocytopenia), nausea/vomiting and peripheral neuropathia. Common adverse events associated with paclitaxel are nausea/vomiting, myelosuppression, arthralgia/myalgia, peripheral neuropathy, alopecia and infections. As expected, these chemo-related toxicities were most frequently observed during the first 6 cycles of therapy. Common AEs associated with bevacizumab are epistaxis, stomatitis, nausea/diarrhoea, hypertension, dyspnoea, headache, arthralgia and fatigue.

In study BO17707, 2 out of 5 cases of grade 5 events were caused by intestinal perforation in the CPB7.5 arm. Intestinal perforation was also the only AE that was reported to AdEERS (SAE) with ≥ 1% higher incidence in a bevacizumab-containing treatment arm relative to the control arm in study GOG-0218 (CPP: 0 patients, 0.0%; CPB15: 7 patients, 1.2%; CPB15+: 6 patients, 1.0%). Intestinal perforation is a well-known risk associated with treatment with bevacizumab.

Benefit-risk balance

- Importance of favourable and unfavourable effects

A reduction in the risk of disease progression or death of 30% and an improvement between 2-4 months in median PFS represents an important benefit to patients. In addition, the 4.1 months benefit of PFS in study GOG-218 has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

When adding bevacizumab to a chemotherapy regimen more adverse events and serious adverse events were reported for the combination arm than for the chemotherapy alone as expected. However, the safety profile for bevacizumab was largely consistent with observations in previous bevacizumab studies. No new safety concerns have been identified.

In conclusion, the AEs encountered with the combination of carboplatin, paclitaxel and bevacizumab are as would be expected from the present knowledge of the safety profile of the three drugs.

Discussion on the benefit-risk balance

Efficacy in terms of progression free survival was demonstrated in both GOG-0218 and BO17707 trials. The adverse events reported were considered acceptable for a patient population with advanced ovarian cancer. The safety profile for bevacizumab is known and generally manageable.

Therefore the CHMP concluded that the benefit-risk balance of Avastin in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer is considered as positive, as the demonstrated statistically significant improvement of PFS outweighs the added toxicity of bevacizumab.

3.4. Avastin (breast cancer)

Benefits

The data from the capecitabine cohort of the AVF3694g (Ribbon-1) study resulted in 2.9 months gain in median PFS (8.6 months in the capecitabine + bevacizumab arm compared with 5.7 months in the capecitabine-placebo arm). The HR was 0.69 ([95% CI, 0.56 to 0.84]; log rank p=0.0002). In support of the primary analysis, the ORR was 35.4% in the capecitabine + bevacizumab arm vs. 23.6% in the capecitabine + placebo arm (p=0.0097).

Uncertainty in the knowledge about the beneficial effects

In the more heavily pretreated patient population in supportive study AVF2119g, the increased ORR was not associated with an improvement in PFS (HR=0.98 [95% CI, 0.77 to 1.25]) or OS (HR=1.08 [95% CI, 0.80 to 1.45]) which may reflect the increasing degree of tumour resistance that develops over time with the successive lines of therapy.

No statistical significance was reached in the PFS results of study AVF3693g (Ribbon-2) .In addition, the ORR was 35.8% in the bevacizumab arm vs. 15.4% in the control arm (p=0.0225) but no statistically significant.

No formal comparison with other standard available first line therapeutic options are made neither the patient population which may eventually benefit from first line capecitabine has been clearly defined.

Risks

The safety profiles of both capecitabine as well as bevacizumab have been well-characterized. Common AEs associated with capecitabine include gastrointestinal disorders, hand-foot syndrome, fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction in patients with pre-existing renal insufficiency and thromboembolism. The addition of bevacizumab to capecitabine has not lead to new safety concerns.

The overall incidence of reported AEs was higher in the combination arm (40.1%) compared to the placebo arm (26.9%). Particularly, the incidences of hypertension, peripheral sensory neuropathy and proteinuria were increased. There were no SAEs with a ≥ 2% difference in incidence between treatment arms. The percentage of deaths unrelated to disease progression was 2.5% in the placebo containing arm vs. 1.5% in the bevacizumab-containing arm.

Concerning the bevacizumab + capecitabine combination, the proportion of patients experiencing grade 3-5 adverse events was 37% *versus* 23% associated with capecitabine + placebo.

Benefit-risk balance

The claimed improvement in PFS associated with the combination of bevacizumab+capecitabine compared to capecitabine alone based on the AVF3694g trial was modest and no important effects have been observed in terms of other clinically relevant endpoints such as OS or health-related quality of life. No important effects were observed in terms of clinical efficacy in study AVF2119g in a relevant patient population.

The bevacizumab + capecitabine combination was associated with significant toxicity. This is of particular relevance since the proposed indication is aimed at first-line treatment of patients with metastatic breast cancer for whom a more tolerable regimen is preferred compared to more active chemotherapy.

In the absence of an established clinical efficacy or other clinically relevant benefits, and considering the significant toxicity of the combination of bevacizumab+capecitabine, the benefit-risk cannot be considered positive in the proposed indication.

Overall conclusion on grounds for re-examination

The CHMP opinion remained negative regarding the previous proposed indication for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are "not preferred".

The CHMP considered that the indication should be more rigorously defined since preference alone is not informative in guiding patient selection and does not necessarily identify patients for whom other treatment options including taxanes and anthracyclines are not available. The CHMP maintained that in a population where patient characteristics allowed treatment options including taxanes and anthracyclines, the benefit-risk of bevacizumab plus capecitabine combination could not be considered positive.

However, the CHMP acknowledged that there is a population in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. The CHMP considered that capecitabine was an acceptable treatment choice and comparator in the subgroup of patients who are not candidates for more aggressive chemotherapy including taxanes or anthracyclines. Such patients include those who may have received anthracyclines and taxanes in the adjuvant treatment setting, who are unlikely to tolerate myelosuppressive treatment, or who are intolerant of cumulative toxicity, elderly patients, or patients with slow-growing disease. Based on this and the data provided, the CHMP agreed that it can be concluded that a clear effect in terms of PFS is seen with the addition of bevacizumab to capecitabine.

Therefore the indication was amended to exclude patients eligible for treatment including taxanes or anthracyclines, as follows: ''*Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received* CHMP variation assessment report EMA/CHMP/443982/2011 Page 51/55 *taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine*''.

The CHMP discussed the clinical relevance of the 2.9 months difference observed in median PFS in this population in AVF3694g (Ribbon-1) trial. The CHMP concluded that this difference was still modest but that the clinical relevance of this effect needs to be assessed in the context of the benefit-risk evaluation in this population for which there are limited alternative treatment options. In terms of other clinically relevant endpoints, the CHMP acknowledged that a detrimental effect in terms of overall survival was unlikely.

The single pivotal trial AVF3694g (Ribbon-1) conducted was sufficiently robust to allow drawing meaningful conclusions in the revised proposed indication. In particular, the effect observed for bevacizumab+capecitabine was considered to be consistent across subgroups and robust to different assumptions explored in sensitivity analyses. The CHMP agreed that the lack of supportive data from study AVF2119g due to the more advanced population included (second and third-line treatment) was no longer considered as a major pitfall in view of the robustness of the pivotal trial and the clear effect seen in terms of PFS.

The overall incidence of reported AEs was higher in the combination arm (40.1%) compared to the placebo arm (26.9%). Particularly, the incidences of hypertension, peripheral sensory neuropathy and proteinuria were increased. However, there were no major differences between treatment groups in terms of SAEs or deaths unrelated to disease progression. The CHMP concluded that despite the toxicity associated with bevacizumab in combination with capecitabine is significant, it is outweighed by a sufficient clinical relevance in terms of PFS for this restricted population and therefore its acceptability has to be assessed in the context of the benefit-risk balance for this restricted population.

Patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate have limited therapeutic options. In this population, the modest effect observed with bevacizumab in combination with capecitabine may be considered of sufficient clinical relevance as it is expected to be associated with benefits in terms of symptom control. Although the addition of bevacizumab resulted in increased toxicity, this was not considered a major concern in view of the clinically relevant effect in this population with limited alternative treatment options. Therefore, the CHMP concluded that in the indication of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate the grounds for negative opinion no longer hold. The CHMP concluded that the benefit-risk balance for bevacizumab in combination with capecitabine as first-line treatment of patients with metastatic breast cancer, in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, is considered positive.

3.5. Baraclude

Twenty-four and 48 week data from study AI463048 demonstrate that entecavir has superior virological efficacy compared to adefovir in a decompensated population with mixed baseline characteristics as regards HBeAg status and lamivudine resistance. All in all, this finding is not unexpected given previous data, and, indeed, entecavir is already a first line recommendation for treatment of patients with CHB and decompensated cirrhosis (EASL guidelines J Hepatol 2009). In terms of improvement of hepatic function, however, no definite advantage was demonstrated within the scope of this trial, perhaps due to the limited duration of on-treatment observation. Longer-term data on change of hepatic function will be provided at Week 96 of the study. There are no clear indications that the safety and tolerability of entecavir would be worse than that of the comparator. The risk benefit balance of entecavir for the present indication is considered positive.

3.6. Carbaglu

In support of this extension of indication one retrospective observational study was submitted. The study design and study population are acceptable considering the rarity of the disease.

Benefits

The reported cases show efficacy of the treatment with Carbaglu on the reduction of ammonia levels in all baseline severity conditions, in all three diagnostic categories (IVA, MMA, PA), in all age groups (neonates, non-neonates), and in both ammonia scavenger medication groups (with and without NH_3 scavengers).

Risks

The number of AEs that are serious and which have unclear relation with drug is proportionally high. However, it should be noted that these are seriously ill subjects and it is difficult to disentangle the cause or consequence in this context. Overall the safety profile is considered acceptable.

Balance

The submitted study shows that use of Carbaglu in all three diagnostic categories (IVA, MMA, PA) results in a clinically relevant ammonia lowering effect without any new, unexpected safety concerns compared to previously reported in the already approved indications. The benefit/risk balance is therefore considered as positive and the variation is approvable.

3.7. Cervarix

In conclusion, non-inferiority of the HPV-16/18 immune response, with respect to GMT ratio at Month 7, was demonstrated for the pooled 9 year old subjects compared to the pooled 10-14 year old subjects and to the pooled 15-25 year old subjects.

These data showed that 9 year old subjects are comparable to subjects 10-14 and 15-25 years of age in terms of seroconversion rates and that the immunological response (GMTs) in 9 year old subjects is non-inferior to the immune response in those older age groups. No clinically relevant differences in the safety profile of the 9 year old subjects who received Cervarix alone or in co-administration with Engerix or Twinrix were observed.

Based on the safety and immunogenicity data in this pooled analysis the CHMP concluded that the risk/benefit balance for Cervarix is favourable to extend the indication to 9 years and adopted the opinion of extending its use to subjects 9 years of age.

3.8. Enbrel (polyarticular juvenile idiopathic arthritis)

Benefits

Beneficial effects

To support the extension of the indication the MAH has submitted a study (based on data extracted from a registry) whose objective was to determine the long-term safety of etanercept with or without other DMARDs in paediatric subjects aged 2 to 18 years with polyarticular course or systemic JRA compared to a control cohort of subjects with polyarticular course or systemic JRA receiving methotrexate with or without other DMARDs.

The beneficial effects of etanercept in older children from the age of 4 years with polyarticular JIA has previously been formally demonstrated to lead to a reduction in the number of active joints, and improvement in physician global assessment and quality of life leading to licensing of that indication.

In study 20021626 the results from the subjects aged 2 to <4 years were similar to the overall population, thereby supporting efficacy in this younger age group.

Although the data are derived from an open label study (based on data extracted from a registry) there is however a clinical need for other treatment options other than methotrexate in the very young children, as a considerable percentage of children may not tolerate MTX. Moreover, it is considered relevant to treat young patients with active arthritis vigorously, to prevent future joint damage. Alternative treatment options of high doses of steroids could cause growth retardation. As no alternative biologicals are available for young children the choice for etanercept may thus be unavoidable in 2- <4 year olds.

Uncertainty in the knowledge about the beneficial effects

The data provided in study 20021626 is supportive of efficacy in the age group 2 to <4 years but because of the open-label nature of the trial, efficacy has not been formally demonstrated. While this is not optimal, recruitment problems have affected other trials in this young age group. As the results of the subpopulation aged 2-<4 years in terms of efficacy were similar to the overall population with polyarticular JIA, these can be considered supportive of efficacy in this group.

An additional area of uncertainty is when to discontinue therapy in non-responders. The MAH has provided an overview of the literature and guidelines available to support discontinuation of treatment in patients who show no response by 4 months of treatment. This additional change in section 4.2 of the SmPC is in line with the evidence provided and the ACR 2011 guidelines.

It is also of interest to explore when and in what manner treatment should be stopped in a patient who has responded well to etanercept. Given the limitations to address this in terms of clinical trial design, the MAH provided literature data and analysis from trials in JIA to show that at present it is not possible to advise on how long a patient should be in a state of low disease activity or remission before deciding on withdrawal of the drug. In addition the high rate of relapse in those who were discontinued was noted, but also it is reassuring that the response to re-treatment in these cases was satisfactory. As unnecessarily long exposure to etanercept should be avoided. The MAH will therefore contact JIA registries to examine whether collection of additional efficacy (effectiveness) information to address this issue is possible as described in the RMP.

Risks

Unfavourable effects

Unfavourable side effects are well documented for etanercept, and highlighted in the SmPC and under continual surveillance as described in the RMP. These include increased risk of infection including TB, reactivation of Hepatitis B, allergic reactions, antibody development to etanercept, development of autoantibodies, blood scrasias, reduced vaccine responses and demyelination. Also an increased risk for the development of malignancies, including lymphoma cannot be excluded.

Unfavourable effects of benzyl alcohol are seen in children under the age of 3 years and include anaphylactoid reactions and additionally in premature neonates, at high levels can results in infant gasping syndrome. Therefore, a benzyl alcohol-free formulation has been registered for Enbrel. As described in the RMP, the MAH will review as part of the annual PSUR the post-marketing data in JIA patients aged 2 to 3 years on a monthly basis after the approval of JIA in children aged 2 to 3 years, until the new 10 mg formulation is available.

Uncertainty in the knowledge about the unfavourable effects

The unfavourable effects on a younger child may be more serious, in that children below the age of 4 years are often naïve to pathogens including common viruses. This could result in more severe primary

viral infections in these children than has been observed in older children. Another area of uncertainty is whether earlier introduction of immunosuppression will lead to an increased risk of malignancy, including virally associated tumour development. The ability to mount an immune response to vaccinations needs to be addressed. The MAH will collect data systematically on the long-term outcomes of JIA patients under the age of 4 years treated with etanercept through the 3 available JIA registries (German JIA registry, Swedish JIA/RA registry [ARTIS], and UK JIA registry [BSPAR]), with particular emphasis on infection risk, malignancies, and vaccination as described in the RMP.

Balance

Importance of favourable and unfavourable effects

For children who need treatment with etanercept and who respond to treatment, the benefit is very significant. With improved control of their disease these children will be expected to have a better quality of life and improved growth.

The benefits of etanercept treatment in JIA for those aged 2 to <4 years is similar to that of the overall population from the study 20021626. Although formal evidence of efficacy has not been demonstrated as this was an open-label trial, the similarity of outcomes between the overall population and the subgroup aged 2 to <4 years were evident. The benefits of etanercept treatment in 2 to <4 years old with polyarticular JIA unresponsive to conventional therapy, result from disease control. As the underlying disease processes of polyarticular JIA in those aged below and above 4 years are the same, the efficacy demonstrated formally in those over the age of 4 years in terms of reduction in joint inflammation, can be expected to be reflected in those under the age of 4 years. This is confirmed by the registry data submitted by the MAH.

Potential risks associated with initiation of etanercept in children as young as 2 years of age include the known side effect profile of etanercept as described in the SmPC and in addition may lead to a higher risk of severe infection and poor immunisation responses in children under the age of 4 years in view of the immaturity of their immune systems. These risks could be monitored and accepted in severe cases with polyarticular JIA unresponsive to standard DMARD therapy. The long term risks associated with immunosuppression also include development of malignancy, a risk which may be higher in the very young children. In view of this the MAH will collect data systematically on long-term outcomes of JIA patients under the age of 4 years treated with etanercept, through the available JIA registries, with particular emphasis on infection risk, malignancies and vaccination responses as described in the RMP.

Benefit-risk balance

Taken together the available efficacy data and the knowledge about the safety profile, as well as the additional pharmacovigilance measures particularly the long-term safety registry, the benefit risk balance is considered positive.

Discussion on the benefit-risk assessment

The well demonstrated efficacy of etanercept in JIA in those over 4 years led to the approval of etanercept in active polyarticular JIA in children aged 4 years and above. The underlying disease processes are the same for children under the age of 4 years with polyarticular JIA. The registry data provided by the MAH support similar efficacy in those aged 2 to <4 years as was seen in the whole population aged 2-18 years. While high quality trial data is usually required for an extension of indication, the difficulty in recruiting young children into trials for this disease has been demonstrated by the MAH. This is likely to at least in part related to the fact that etanercept is approved in children with polyarticular JIA from the age of 4 years and in the US from the age of 2 years. The benefit of treatment in young children under the age of 4 with active disease, where no alternatives exist is

expected to lead to a reduction in joint destruction and improved quality of life. The known risks of etanercept are highlighted in the SmPC and the RMP, but additional concerns relate to its use in those under the age of 4 years. The risks of infection and the possibility that the risk of malignancy will be increased relatively more the younger the age of onset of treatment remain concerns. These concerns will be monitored with long-term active pharmacovigilance activity as described in the RMP. The balance in a subject with active polyarticular JIA is in favour of treatment provided that the warnings in the SmPC are followed and the subject is followed long-term for assessment of safety, particularly the development of malignancy.

The benefits of earlier introduction of treatment with etanercept in polyarticular JIA patients aged 2 to 4 years who have not tolerated to, have a contra-indication to or do not respond to non-biological DMARD therapy is expected to provide similar benefit as has been formally demonstrated in children aged 4-18 years. Long-term disease associated morbidity is linked to the speed of achieving acute disease control.

Earlier control of resistant disease associated morbidity is expected to lead to less joint destruction and a favourable clinical outcome in terms of joint function, development and quality of life.

Based on the CHMP review of data on safety and efficacy, the CHMP considered that the risk-benefit balance of Enbrel in the treatment of polyarticular JIA in children from the age of 2 to <4 years was positive.

The following indication is therefore agreed for section 4.1 of the SmPC:

Polyarticular juvenile idiopathic arthritis

Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of **2** years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than **2** years.

3.9. Enbrel (paediatric plaque psoriasis)

Benefits

Beneficial effects

The double-blind, placebo controlled study that served as the basis for the approval in paediatric patients with psoriasis from the age of 8 years, study 20030211, demonstrated that etanercept at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg QW) was associated with significantly greater improvements in the measures of psoriasis compared with placebo. Subgroup analyses were subsequently performed to describe the efficacy and safety profile of etanercept in a subpopulation of paediatric psoriasis subjects aged 6-7 years in study 20030211.

The improvements in efficacy observed during study 20030211 in subjects aged 6-7 years were maintained through 96 weeks of treatment in the extension study 20050111. The data provided in study 20050111 is supportive of efficacy in the age group 6-7 years old. Since the results of this subgroup in terms of efficacy were similar to the overall population, it is acceptable to conclude that these results can be considered supportive of efficacy in this group.

Uncertainty in the knowledge about the beneficial effects

Because the efficacy results are from a small number of subjects (n=17 for the 36 week study and n=14 for the 96 week study), the evidence for efficacy is limited. However what has been shown is

that the efficacy responses were well maintained in the subjects aged 6-7 years who received etanercept through 96 weeks in the extension study. Furthermore, for all endpoints the results for the 6-7 year group are consistent with the overall population. As the mechanism of the disease is expected to be the same in 6-7 year olds and in those over 8 years, it is reasonable to extrapolate efficacy from the older paediatric population to those aged 6-7 years. The consistency of the data over time and across age ranges is therefore supportive to the conclusion that the available data are sufficient.

Risks

Unfavourable effects

The safety profile in the age group 6-7 years appears is generally similar to the one observed for the population from 8 years of age, for which the product is already approved. The unfavourable effects are well documented, highlighted in the SmPC and under continual surveillance as described in the RMP. These include increased risk of infection including TB, reactivation of Hepatitis B, allergic reactions, antibody development to etanercept, development of autoantibodies, blood dyscrasias, reduced vaccine responses and demyelination. Also an increased risk for the development of malignancies, including lymphoma cannot be excluded. The SmPC and the Risk Management Plan adequately address these safety-related topics.

Uncertainty in the knowledge about the unfavourable effects

In general there are uncertainties with regard to the use of immunosuppressants in children where an earlier introduction of immunosuppression may lead to an increased risk of malignancy, including virally associated tumour development. In order to collect more information in this patient population the MAH has already set up the PURPOSE registry (a multicenter, long-term, prospective, observational, cohort study conducted to evaluate the long term safety and effectiveness of etanercept prescribed by dermatologists to children for the treatment of plaque psoriasis) as part of the initial approval of the use of etanercept in paediatric plaque psoriasis. This registry also covers the age range of the present extension application, and allows the identification of any common serious or new potentially unrecognized ADRs in paediatric plaque psoriasis patients who received etanercept. The registry will recruit between 100-200 patients and is currently enrolling patients. Data from this ongoing registry will address the safety concerns of etanercept in paediatric psoriasis. The MAH provides interim progress reports annually as part of the PSUR and the RMP. The MAH will submit the final report at the completion of the eight year registry as described in the RMP.

Balance

Importance of favourable and unfavourable effects

The balance of favourable and unfavourable effects has to take into account that the extension of age is from 8 years to 6 years and is supported by randomised controlled data albeit in a small number of patients and long-term open label data which is supportive of maintenance of efficacy.

Furthermore, from a clinical point of view, in patients in which all other available therapeutics alternatives have failed, and without any other viable alternatives, the use of Enbrel constitutes a significant advantage for these patients with severe plaque psoriasis in terms of disease control (PASI, PGA). The disadvantages include the known side effects of etanercept which are highlighted in the SmPC and under continued pharmacovigilance as detailed in the RMP.

Benefit-risk balance

The benefit of etanercept in the treatment plaque psoriasis in patients between the ages of 6-7 years was demonstrated in study 20030211 in a limited number of patients. These data were further substantiated through the open label study 20050111, where the efficacy was maintained over time

and the benefits of etanercept treatment in paediatric plaque psoriasis for those aged 6-7 years was similar to that of the overall population. The safety profile in the age group 6-7 years appears to be similar to the paediatric population for which the use of the product is already approved. A registry will collect further long-terms safety data. The benefit-risk balance is therefore considered favourable.

Discussion on the benefit-risk assessment

The efficacy of etanercept in plaque psoriasis in children aged 8 -17 years was demonstrated in study 20030211 and this led to the approval of etanercept in a plaque psoriasis children aged 8 years and above. In addition although the efficacy in children under the age of 8 years was also shown in study 20030211, the numbers were very limited and the length of the trial was 48 weeks. The additional long-term data from the open label study 20050111 in the paediatric population overall and for the subset of patients who at any time were between the ages of 6 and 8 years, are supportive of both safety and maintenance of efficacy in the 6-7 year old subgroup. The maintenance of efficacy and safety profile for the 6-7 year olds and are similar to the results of the overall paediatric population in the open label study. The availability of an effective treatment in children where no alternative therapeutic options are available is considered a benefit.

The safety profile for those aged 6-7 years did not differ from the overall paediatric population in the open label study for up to 96 weeks. These risks are highlighted in the SmPC and are monitored with the ongoing study 20050111 (for up to 5 years) and by pharmacovigilance activity and the PURPOSE registry as described in the RMP.

The benefits of earlier introduction of treatment with etanercept in paediatric patients aged 6-7 years with severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies is expected to provide similar benefit as has been formally demonstrated in children aged 8-18 years. The earlier control of resistant disease is expected to lead to a favourable clinical outcome in terms of symptom control, development and quality of life. For children who need treatment with etanercept and who respond to treatment, the benefit is very significant. With improved control of their disease these children will be expected to have a better quality of life and improved growth.

Based on the CHMP review of data on safety and efficacy, the CHMP considered that the risk-benefit balance of Enbrel in the treatment of paediatric plaque psoriasis in children from the age of 6 years was positive.

The following indication is therefore agreed for section 4.1 of the SmPC:

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of **6** years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

3.10. Gardasil

Benefits:

Demonstrated benefits

In Protocol 020, administration of the qHPV vaccine in a 3-dose vaccination regimen to 16 to 26 year old men was shown to be highly efficacious in preventing HPV 6/11-related external genital warts in the primary analysis**.** The end-of study results showed maintenance of vaccine efficacy over a median

duration of follow-up of 35.3 months for the overall study population. Data from study 020 also demonstrated that there is a significant reduction in the overall burden of HPV-related external genital warts through qHPV vaccination resulting in statistically significant reductions of biopsies and therapies related to EGLs.

The magnitude of vaccine efficacy against genital warts in males was comparable to that previously shown for females. HPV 6 and HPV 11 seem to play a more important role in young men than in young women. The burden of genital warts is significant in males. Although they are usually benign, genital warts cause pain, discomfort, and pruritus, are highly infectious and result in social stigmatization and psychosocial burden in affected patients.

In the MSM substudy of Protocol 020, there were few cases of anal premalignant lesions (AIN 2/3) but significant efficacy was demonstrated. Also for the most relevant endpoint, HPV 16/18-related AIN 2/3, efficacy was high (86.6% (95%CI: 0.0, 99.7), although statistical significance was barely reached. Supporting evidence was the consistency of the vaccine effect across all severity grades of AIN and all populations. In addition, a *post-hoc* analysis in HPV naïve MSM showed high efficacy against anal persistent infection due to HPV 16 and 18 (VE 95% and 100%, respectively). Extrapolation of data from anal disease in MSM to anal HPV infection and related disease in heterosexual men and women is accepted.

The vaccine-induced immune responses in men aged 16-26 years were robust, and generally comparable to those in women aged 16-26 years. As in females, the low persistence of GMTs and seropositivity as measured by cLIA for HPV 18 at Month 36 did not translate into loss of efficacy, but will have to be closely monitored in the future. On the basis of immunogenicity bridging, using Protocols 016 and 018, protection against genital warts in adult males can be inferred in 9-15 year old males

The qHPV vaccine when administered to men 16 to 26 years of age was well-tolerated, and the clinical AE profile exhibited was consistent with that in females. No new or significant safety issues were identified.

Potential benefits

To date there are no effective preventive strategies against extragenital or anal disease in men available. No standardised screening for HPV infection or early detection premalignant genital/anal disease is employed in men apart from certain high risk groups. Thus, there may be an unmet medical and public health need. However, since the incidence of anal cancer in the overall population is very low, the absolute benefit of vaccinating all boys/adolescents prior to sexual debut is likely to be very limited.

Studies support the important role of men in the transmission of HPV to women. Published studies have shown the association between men's sexual behaviour and cervical cancer in women and also indicate high prevalence of HPV-associated PIN in sexual partners of women with CIN. In the pivotal study 020, data demonstrated that the qHPV vaccine was efficacious in preventing HPV 16/18-related persistent infection.

Risks and uncertainties

The anti-HPV immune responses in MSM were lower than those observed in heterosexual men. The consequence of these lower antibody responses in MSM for long-term efficacy is not known, since no minimum anti-HPV level that confers protection has been defined.

The limitations and risks identified for the male vaccination program are consistent with those identified in previous variations for the qHPV vaccine. Two key limitations of the data to date include:

(1) The long-term duration of protection induced by the qHPV vaccine remains to be determined; to provide additional data a sentinel cohort of adolescent boys and girls is being followed to assess vaccine effectiveness up to 10 years following study entry. In addition, for evaluation of long term vaccine efficacy in the male population, Protocol 020 subjects will be enrolled in an extension for 10 years of follow-up from entry into the original study. These data will also indicate the possible need for a booster dose of the vaccine.

(2) The qHPV vaccine safety database is insufficient to detect safety signals with respect to rare conditions (i.e., medical conditions occurring at a background rate of <1:10,000); to date the post-marketing safety experience with the qHPV vaccine is consistent with the safety profile observed in clinical trials.

The 10-yr extension of study 020 and the Adolescent Vaccine Effectiveness Study will provide long-term safety data. Although the types of adverse experiences reported in males do not suggest a unique safety concern for that gender, the risks have to be further evaluated in the post-marketing program as outlined in the RMP to allow a firm conclusion to be drawn.

All autoimmune reactions including arthralgia and vitiligo should be continuously closely monitored and reported on in future PSURs.

HPV type replacement with oncogenic non-vaccine HPV types is considered as an important potential risk and a detailed plan to address this issue is included in the RMP.

There are no data for use in populations at high risk for HPV infection, such as immunosuppressed patients including HIV-infected individuals. Any use of qHPV vaccine in these populations may not provide satisfactory protection or there will an obvious risk for breakthrough infections.

Balance conclusion:

Gardasil/Silgard is currently approved for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic HPV types and prevention of genital warts causally related to specific HPV types. Even though this indication is based on data from the female population, the use in boys/men to prevent genital warts is not contraindicated even though it has been stated in the SmPC section 5.1 that "*Immunogenicity and safety of Gardasil/Silgard have been demonstrated in 9- to 15-year-old boys. Protective efficacy has not been evaluated in males"*.

The purpose of this variation was to add prevention of "premalignant anal lesions and anal cancer" in the indication including the general population of both men and women as well as reflect the current experience in males in sections 4.8 and 5.1 of the SmPC. In support of the extension of the indication results in MSM in study 020 were assessed. It has been agreed that the results can be extrapolated from the MSM population to the general population, including both heterosexual men as well as females. The rates of anal infection and anal disease are higher in the MSM compared to the general population. However, since sexual identity will not be evident until after sexual debut, implicating a possible high prevalence of prevalent HPV infection, it has been considered that the maximum effect of vaccination would be obtained in virginal (or at least pre-pubertal) boys.

Overall, in the EU, the annual incidence rate of anal cancer is estimated to vary between 0.3 and 1.2 per 100,000 in men and between 0.5 and 2.9 per 100,000 in women. Thus, the incidence of anal cancer in the general population of men and women is lower relative to the incidence in MSM, and the overall number of cases of anal cancer that occur annually is lower than for other common HPV-related malignancies. This implicates that, in the general population, the vaccine may be offered without any benefit as regards the indication to prevent anal cancer.

At the oral explanation, the MAH presented estimations of reduction of cases of anal cancer over 50 years (n=1840) if males would be vaccinated, but it was unclear how many males would have to be vaccinated to achieve this goal. Even though the safety profile in males is not believed to be different compared to females, and it is agreed that based on current knowledge, the safety profile seems innocuous, unexpected adverse events always constitutes an uncertainty and therefore, the CHMP concluded that the expected very limited benefit in the general population with respect to prevention of anal cancer, is not expected to outweigh potential safety issues. Therefore, the extension of the indication to include premalignant anal lesions and anal cancer is therefore not considered as approvable.

Vaccine efficacy against genital warts has been convincingly demonstrated in both the PPE and FAS populations and the qHPV indication for males should focus on these lesions. Thus, the CHMP recommended revising the initial proposed indication external genital lesions to genital warts during the procedure.

The preventive effect against genital warts is considered to be of clinical relevance; therefore section 5.1 of the SmPC includes a description of study 020 with main focus on results in the main study in support of the revised indication. A short and balanced description of the results of the MSM study was also included in 5.1.

The planned 10 year follow-up of P020 as outlined in the RMP is considered critical to assess long-term durability of immunogenicity and efficacy in males and to clarify if and when a booster dose will be needed in the future.

Based on the above consideration, the CHMP concluded that the following MAH's proposed change is endorsed for the following change in section 4.1 of the SmPC with the agreed revision

- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of ~~**external genital lesions including**~~ **genital warts** (condyloma acuminata) caused by HPV types 6, 11, 16, and 18.

The CHMP further concluded that the following MAH's proposed changes are not endorsed for the following changes in section 4.1 of the SmPC and related section of the PL:

- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of premalignant anal lesions caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of anal cancer caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of persistent infection due to HPV types 6, 11, 16, and 18.

3.11. Herceptin (adjuvant breast cancer)

Benefits

- Beneficial effects

Adjuvant trastuzumab was associated with a statistically significant and clinically relevant effect on disease free survival. In the joint analysis of the NCCTG 9831 and NSABP B-31 trials, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence (primary endpoint, DFS). The difference in terms of DFS in favour of the Herceptin arm was 6% or 9%

at 3 years, depending on the studies. With the longest follow-up available (median of 65 months), it was estimated to be 9% at 5 years.

The effect was observed in both node-negative and node-positive tumours, and was independent of age or menopausal status, type of surgery/radiation therapy, and main tumour characteristics such as hormonal receptor status, size, or histological grade.

In addition a clinically relevant effect on overall survival has been observed. The difference in terms of OS was above 2% at 3 years in all studies and with the longest follow-up available, it was estimated to be 5% at 5 years.

The superiority of TCH or DCarbH treatments was also observed in one trial when compared to the control regimen (AC→T) with a difference in terms of DFS estimated to be 5% at 3 years (6% at 5 years). The difference in terms of OS was above 2% at 3 years and with the longest follow-up available, it was estimated to be 4% at 5 years.

Adjuvant treatment of trastuzumab given concurrently compared to trastuzumab given sequentially after completion of chemotherapy shortened the therapy by around 3 months (from 18 months to 15 months). With the DCarbH regimen the duration of intravenous adjuvant therapy is also shortened by around 3 months compared with the AC →T+H regimens and by around 6 months compared with sequential trastuzumab.

- Uncertainty in the knowledge about the beneficial effects

No uncertainties have been identified about the benefit of the concurrent use of trastuzumab with chemotherapy (doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or as part of a treatment regimen in combination with docetaxel and carboplatin) in the adjuvant treatment of patients with HER2-positive early breast cancer. All tested chemotherapy protocols in the provided randomised trials in combination with trastuzumab increased progression free survival and decreased the risk for relapse.

A direct comparison of the different chemotherapy protocols was not available. It is therefore possible that there are differences in efficacy for the different protocols, but the clinical relevance of these differences are unknown. Patient risk factors may determine the choice of the regimen and should be assessed in a case by case base according to the current recommendations available in the SmPC.

Risks

- Unfavourable effects

Important risks that have been identified in the adjuvant treatment with trastuzumab are cardiac events including death from cardiac compromise, infection, neutropenia, infusion reactions and pulmonary reactions.

Concurrent administration of trastuzumab with a taxane increased a certain number of taxane-related toxicities, including haematological toxicities. Most importantly, cardiac toxicity appeared worse than with sequential administration. When taking into account both symptomatic CHF events and asymptomatic declines in LVEF, the cumulative incidence of cardiac dysfunction events - depending on the definition of LVEF decline - reached at 3 years 36% (AC →T+H) vs. 24% (for AC →T) in the B-31 and N9831 studies and 11% vs. 5%, respectively, in the BCIRG 006 study. Results were intermediate with sequential administration.

All adverse reactions and risks associated with the treatment have been addressed adequately in the SmPC.

- Uncertainty in the knowledge about the unfavourable effects

It is not clear whether a true difference exists in the occurrence of cardiac events between different chemotherapy protocols in combination with trastuzumab. AE collection was not standardised and is not comparable across trials. Only one chemotherapy regimen (DCarbH or TCH) tested in BCIRG006 appears to have a considerably lower risk of cardiac events than the other protocols. It is at present unknown whether the rate of patients with cardiac compromise will continue to rise in the future. To address the recovery of the cardiac function after treatment with trastuzumab the MAH has committed to provide further follow-up data on LVEF from studies BCIRG 006 and N9831. In addition, details of evolution of symptomatic events and asymptomatic declines in ejection fraction with the need and changes in the treatment of these events will be provided by the MAH from an ongoing observational study (OHERA/BO20652) as a post-authorisation commitment.

Moreover, long-term monitoring of cardiac safety was considered necessary and the MAH is currently addressing this through the extended follow-up of four large adjuvant trastuzumab studies and the large prospective observational study (OHERA/BO20652) to further investigate cardiac safety in 3,800 patients enrolled in a community hospital setting in Europe. The MAH has been also requested to perform a study to address long-term cardiac safety using cardiovascular magnetic resonance imaging (CMR) as a post-authorisation commitment.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Survival without recurrence of disease is of utmost importance to the patient in the adjuvant setting. The predominant short term risk, i.e. non-fatal cardiac AE, infusion reactions, infections appear less important in this context. Long term or later occurring consequences of cardiac compromise could be of major importance to the patient later in life. Given that the majority of patients will not have a relapse (at least according to current data) the issue of cardiac damage in later life could become increasingly important. The long-term consequences of the declines in LVEF observed after trastuzumab therapy are still not well understood while several large scale studies have proven beyond doubt that asymptomatic LV dysfunction irrespective of original injury has poor prognosis.

In order to better characterise the benefit-risk balance of trastuzumab, a combined analysis of DFS and cardiac dysfunction events was assessed. With beneficial effects in terms of DFS and long-lasting cardiac dysfunction, this analysis becomes even more valuable in order to better define and quantify the margin of benefit allowed by trastuzumab treatment.

In addition, the new anthracycline-free regimen proposed may decrease the long-term and life-altering toxicities (CHF or acute leukemia) of anthracycline-containing regimens.

- Benefit-risk balance

The benefit-risk balance of addition of trastuzumab to adjuvant chemotherapy protocols is favourable and the beneficial effects as reflected in increased PFS and OS outweigh the unfavourable effects.

3.12. Humira

One pivotal study was performed with adalimumab in children/adolescents aged 4-17 years with polyarticular JIA. Subjects were stratified according to MTX use or no MTX (either naïve, inadequate responders or intolerant). Following an open label lead-in phase where all patients received adalimumab, 24 mg/m^2 BSA, responders were at week 16 randomised into a double-blind withdrawal

phase of 32 weeks, where the primary endpoint (the proportion of subjects in the non-MTX stratum with a disease flare) was assessed. In this phase, 58 subjects were enrolled into the non-MTX stratum and 75 into the MTX-stratum. The design was chosen from ethical reasons. The study population and clinical endpoints were adequate.

After the blinded phase, patients could continue on open label BSA dosing. Thereafter, patients were switched to open label fixed dosing of 20 mg (subjects up to 30 kg body weight) or 40 mg (> 30 kg) eow. The data presented allowed fixed dose of 40 mg from the age of 13 years. For younger children, dosing based on BSA was recommended. The MAH has now developed a presentation which allows for the accurate dosing according to BSA.

Benefit

In the open initial phase, the response rate, according to the predefined 30% improvement criteria, was 94% with MTX + adalimumab and 74% in the adalimimab monotherapy group. There were more responders among the patients with "active disease despite MTX" (i.e. the group given combination therapy) compared with patients without MTX, and more patients without MTX discontinued the open phase, which indicate an increased efficacy with combination therapy. Therefore it was considered that combination therapy is the primary recommendation, but in case of MTX intolerance, monotherapy might be an option.

During the blinded withdrawal phase, the primary endpoint, proportion of subjects with disease flare in the non-MTX stratum, as well as the same endpoint in the MTX stratum, was statistically significantly in favour of adalimumab. The low threshold for flare and the use of imputation have to be taken into account when analysing the results of the primary efficacy. Overall, it is accepted that adalimumab prevents disease flares compared to placebo but due to the complex trial design, the superiority of adalimumab over placebo in the treatment of JIA may be overestimated. Appropriate wording in the SmPC reduces the risk of patients not responding to receive continued treatment: the product information advises caution if a patient does not respond within 12 weeks of treatment; furthermore, a registry aiming to collect more data in this regard has been set up following the previous procedure (EMEA/H/C/000481/H/C/39). It was considered of importance to collect efficacy data in the registry setting, which the MAH agreed to undertake. The registry is ongoing.

In addition to the higher percentage of responders in the lead-in phase, the number of discontinuations was higher in the non-MTX during the initial phase, and there was a higher number of responders achieving the more stricter Ped ARC50/70 criteria in the combination group. Anti-adalimumab antibodies developed in a higher number in the non-MTX group, 25.6% versus 5.9%, which justifies follow-up on the long term efficacy (registry ongoing) also raises concerns regarding long term efficacy. Finally, the pharmacokinetic data indicate a higher adalimumab plasma level in the combination group.

Overall, these data support combination therapy with MTX. Combination therapy is the primary recommendation in the indication.

Risks

The safety profile of an anti-TNF agent is well established, with infections as one main concern. No new safety signals were found in the performed study. The three most frequently reported AEs by MedDRA preferred term included upper respiratory tract infection, viral infection, and injection site reactions. No cases of death, malignancies, CHF, CNS demyelinating diseases, opportunistic infections, serious blood dyscrasias, or lupus-like reactions were reported. To further assess the long-term safety, for which at present the database is limited, a registry has been set up, which also monitors the development of malignancies. Safety data obtained during the OL LI, DB, and OLE BSA phases, during which dosing

was based on BSA (24 mg/m2 up to a total dose of 40 mg eow), were comparable to the safety data obtained during the OLE FD phase. No apparent difference in type or rate of AEs was observed in those subjects who were determined to be AAA positive compared to those that were AAA negative. Overall, safety data obtained in this adalimumab trial in pediatric JIA subjects are consistent with those expected in the adult RA population.

The RMP is acceptable, the proposed Paediatric vial educational programme has not considered necessary for inclusion in the RMP. The MAH has a registry ongoing where both safety and effectiveness data are collected. The MAH will follow subjects for 5 years for all events specified in the Registry protocol and additional 5-years on an annual basis to collect events of CHF and Malignancies.

The MAH took the opportunity to remove the Alert Card from the annexe III-A. This is acceptable as the Alert Card is not part of the pack and is not included in the carton. Nevertheless the patient alert card must remain in use and is part of the RMP.

Benefit-risk balance

The MAH applies with dosing instructions to allow for dosing according to the BSA posology used in the clinical study for children younger than 13 years. The reason is that only BSA dosing has been adequately documented for those children. Thus, with this new option, it is possible to administer an appropriate dose also to this age group.

Efficacy has been sufficiently demonstrated with the body surface area dosing of 24 mg/m^2. There are tendencies of better efficacy with a combination of adalimumab and MTX. The indication was revised and combination therapy with MTX is the primary option. A fixed dose of 40 mg from the age of 13 years was agreed. With the availability of an option to use BSA dosing in the younger children, also adequate dosing of children aged 4-12 years is ensured.

The safety profile demonstrated in the study shows no unexpected findings, but long-term safety remains a concern to be followed in the ongoing registry. To conclude, the benefit / risk balance for the treatment of subjects aged 4-12 years, with active polyarticular juvenile idiopathic arthritis, who have inadequate response to one or more DMARDs, is positive.

3.13. INOmax

Benefits

- Beneficial effects

The MAH has presented a brief summary of the biology of Nitric Oxide (NO) as an endogenous signaling molecule playing essential roles in a variety of biological systems, and particularly in the control of vascular tone. Nitric oxide was identified as the "endothelial derived relaxing factor" in the years 1980. The first therapeutic application of NO, by inhalation, was reported in 1991 to decrease pulmonary vascular resistance (PVR) in patients with primary pulmonary hypertension. Inhaled NO has been used in the intensive care unit (ICU) setting to decrease PVR in patients with severe lung injury. This intervention was accompanied by variable improvements in arterial oxygenation, which was explained by improved ventilation-perfusion relationships due to preferential decrease in PVR in the best aerated lung regions.

Pulmonary hypertensive crisis during or in the postoperative course of cardiac surgery is an interesting indication of inhaled NO. The condition is life-threatening. Extensive off-label experience of inhaled NO

in the ICU's has established its efficacy and its safety in this indication. As such, the treatment is included in the recommendations of European and North American expert consensus documents on the treatment of pulmonary hypertension. The rationale behind these recommendations has been adequately summarised in the application. Thus doses from 10-40 ppm of inhaled NO have been shown to be safe and effective. The strategy of adjustment to the lowest dose allowing for the desired hemodynamic effects is well established.

There have been a total of 20 randomised controlled trials of inhaled NO in acute pulmonary hypertension on cardiac surgery: 13 in 588 adult patients, 7 in 299 pediatric patients.These publications help to understand the usefulness of nitric oxide gas in controlling a life threatening condition namely pulmonary hypertension adults and children following cardiac surgery. The Applicant has identified key publications which establish dose and efficacy of monotherapy with NO versus standard therapies milrinone and prostacyclin and PGE1 in adults. In children key publications have established usefulness in younger children of inhaled NO as a monotherapy (children aged on average 3months) and in combination with milrenone (children aged on average 5.5yrs).

Data showing haemodynamic efficacy in severe pulmonary hypertension have been presented in detail by the MAH in a fair and balanced manner, with appropriate interpretation.

- Uncertainty in the knowledge about the beneficial effects

Each of the reported studies is relatively small, and there has been variability in end points. This is understandable as mortality studies are extremely difficult in these patients, placebo controls could be unethical, and there is no consensus on a single endpoint as the most adequate surrogate measure of the disease. Also, in the acute unstable situation of the pulmonary hypertensive crisis, physicians in care have to react quickly with decision making essentially guided by pathophysiological reasoning. Nevertheless, the available controlled and uncontrolled evidence is largely in favour of efficacy with minimal and manageable toxicity of inhaled NO in pulmonary hypertensive crisis on cardiac surgery.

Risks

- Unfavourable effects

Approximately 300,000 patients have been exposed until now to various durations of inhaled NO. There has been no signal that the treatment (including its formulation, and administration device) is associated with significant safety problems.

Alternative therapies are much more difficult to handle than inhaled NO because of a variety of side effects, of which the most significant are systemic hypotension and alteration of pulmonary gas exchange. None of these alternative therapies show greater efficacy than inhaled NO in controlling acute severe pulmonary hypertension.

The summary of safety data has not highlighted major specific adverse events which could be associated exclusively with the use of NO in post cardiac surgery patients, be they either children or adults. It is evident that the customary precautions of use of inhaled NO apply with in addition the issues of weaning which have been specified in the SPC. It must be remembered that these patients are associated with high risk so adverse event reporting will be higher with higher co-morbities and mortalities. While the key publications used in the submission do not adequately cover this, some is covered by the two company sponsored studies. Numbers reported will be small because of the smaller number so of patients who undergo cardiac surgery.

The SPC includes information on the prevention and management of side effects reportedly associated with inhaled NO, that is methaemoglobinaemia, generation of nitrogen dioxide, rebound pulmonary

hypertension, left heart failure with increased pulmonary capillary pressure, and platelet dysfunction with increased bleeding time. Warnings about pregnancy and lactation (unknown effects of inhaled NO) are also included.

- Uncertainty in the knowledge about the unfavourable effects

A Risk Management Plan has been provided in conjunction with this variation to extend the indication for INOmax. The RMP addresses the following identified risks:

- Methaemoglobinaemia
- Formation of nitrogen oxides
- Rebound effect
- Risk of acute cardiac failure (contraindication or warning in different patient populations)
- Risk of critical failure of the delivery system

In addition, the RMP for INOmax also focuses on the potential risks of NO treatment, about which there is some uncertainty:

- Risk of bleedings and haemostasis disorder
- Risk of additive effects from the combined use with other vasodilators acting on the cGMP or cAMP pathway

NO has been used in approximately 300,000 patients to date, and the identified risks are well characterised. The uncertainty surrounding the risks of bleeding and combination use with other vasodilators, along with the better characterised identified risks are managed via information in the SmPC (warnings and precautions, and recommendations for monitoring); training of healthcare personnel who will administer NO; and information provided in a pocket guideline for all relevant healthcare professionals.

The above described risks and the complete overall safety profile of INOmax will be monitored in Periodic Safety Update Reports, which will initially be submitted at 6 monthly intervals. The PSURs will include information on adverse reaction reports (including reports of device failure), clinical trials and the published literature, and are anticipated to further increase our knowledge of the unfavourable effects of NO.

Benefit-Risk Balance

The benefit-risk balance for the use of inhaled NO in pulmonary hypertension peri- and post heart surgery, although based primarily on publications, is considered positive in adults since no major safety or efficacy considerations have been identified and the use presents itself as an extension to currently well established use for pulmonary hypertension in Intensive Care. In the case of the paediatric population the supporting data does not appear as robust making a positive benefit risk balance difficult. However, in the absence of robust information we are left with the choice of non-approval of a paediatric indication for a potentially life-saving drug due to lack of data in age groups in which the drug is less frequently used, or a more pragmatic approach. Overall the latter appears preferable as:

- The proposed posology in children (initiation at 10 ppm, titration between 5-20 ppm based upon response) is generally based on the available data. Although the lower dose (5 ppm) does not

appear to have been employed in the key paediatric studies it is in the effective range on the basis of available physiological data and is a "non-toxic" dose.

- Cardiac surgery in children is principally performed in younger children for whom the proposed posology is well supported by Miller's and Cai's studies.
- Physicians administering NO are likely to be conversant with the principle of titration to effect and the risks of NO therapy particularly circulatory compromise secondary to lowered pulmonary vascular resistance and methaemoglobinaemia both of which are detailed in the SPC .
- The SPC statement regarding the limited clinical data in 12-17 year olds should alert physicians to the possibility that the proposed posology may be ineffective in this age group

Taking the above into account, the risk benefit balance for INOmax, in conjunction with ventilatory support and other appropriate agents as part of the treatment of peri- and post-operative pulmonary hypertension in adults and children in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation, is considered positive.

The following indication wording is therefore agreed for section 4.1 of the SmPC (additions highlighted):

INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:

- for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

3.14. Kiovig

Benefits

Beneficial effects

Multifocal motor neuropathy is a recently-described motor neuropathy with an incidence of (about) 6 per million people and that affects adults in the age range 20 to 55yrs. Men are more commonly affected than women. There are not any known pre-disposing factors and the underlying aetiology is uncertain. Motor nerves are affected in a piece-meal fashion leading to an asymmetric weakness that (in about 70% of cases) presents with weakness of the intrinsic muscles of a hand. Symptoms are more evident than signs in the initial stages of the illness. The natural history of the disease is for slowly progressive weakness and atrophy of affected muscles with associated impaired quality of life.

Diagnosis of multifocal motor neuropathy is by a combination of a typical clinical history supplemented by nerve conduction studies and assessment of muscle strength. The presence of anti-GM antibodies may supplement the diagnosis.

Acceptable outcome measures of treatment of multifocal motor neuropathy would be increased muscle strength (of those muscles affected) and less functional disability associated with improved quality of life.

Evidence of benefit of treatment with IVIg is thus far limited. For this reason, all applications for IVIg in the indication for multifocal motor neuropathy required to be accompanied by persuasive data on increased muscle strength in response to treatment.

In the present application, the results from two, prospective, uncontrolled, open-label, investigator-initiated trials were submitted showing that intermittent intravenous infusion of KIOVIG in (i) the initiation and (ii) maintenance of treatment of patients with multifocal motor neuropathy resulted in increased muscle strength (assessed by MRC scores, dynamometry and grip strength) and a reduction in reported disability (as assessed by the Guy's scale of disability and self-assessment).

The initiation trial involved 8 subjects who were naïve to treatment with IVIg. Patients received a five-day course of KIOVIG at a cumulative dose of 2g/kg body weight. Maintenance doses for the 7 subjects entering the long-term follow-up phase of the study were chosen by individual response. MRC sum scores were measured at baseline, after the first full course of IVIg (cumulative dose 2g/kg) and after the last follow-up examination of the long-term treatment phase. Additionally, a descriptive analysis of the response to KIOVIG on functional impairment (regarding daily life activities) was presented for each of the eight subjects. Subjects achieved up to 4 points increase in MRC score in response to Kiovig treatment: response was persistent for the duration of the trial (12 months).

The maintenance trial involved 20 subjects who were transferred from GAMMAGARD s/d (an alternate IVIg preparation licensed for use in MMN in the Netherlands) to KIOVIG at an equivalent dose. Treatment with KIOVIG was shown to maintain muscle strength for the duration of the conversion (9 months).

The MAH also submitted a review of published literature on the use of IVIg in the management of multifocal motor neuropathy.

The numbers of subjects enrolled into the two studies submitted were too small to consider sub-group analysis. The applicant justified not doing a comparator study on the grounds that cyclophosphamide (the only recognised comparator with reported efficacy) would be easy for investigator and subject to tell apart from KIOVIG on the basis of side-effects.

Overall, the data package provided was considered sufficient to demonstrate the efficacy and safety of KIOVIG in MMN, and in line with the requirements of the EMA guideline on clinical investigation of IVIgs.

It was considered that additional data submitted by the applicant on the efficacy of KIOVIG use in CIDP and on the Dutch national database of subjects with multifocal motor neuropathy did not support the current application.

Furthermore, the MAH provided information showing that home-infusion of KIOVIG was widely accepted by patients and that although only a minority self-infused, patients welcomed advantages of home-treatment such as time gain and convenience. Occurrence, frequency and severity of adverse events in home treated patients were comparable to those in the hospital setting.

As home IVIg administration has been in existence since the 1980s, and guidance material already exists, no additional risks associated with KIOVIG for MMN or any other indication foreseen, and risk minimisation activities are therefore not required. However, the available safety information on home infusion and criteria for patient selection should be included in the next RMP update.

Uncertainty in the knowledge about the beneficial effects

The mechanism of action of IVIgs in MMN has not been elucidated, leaving an uncertainty as to the pharmacodynamics. This is true for all "immunomodulatory" indications and therefore more basic research would be of essence. Nevertheless, the use of IVIg in MMN is recommended in relevant treatment guidelines, and some efficacy data has been obtained for different formulations.

The data on the efficacy of KIOVIG for the treatment of patients with MMN was derived from two open-label, single arm clinical trials. There was no dose finding study; however, dose and dosing intervals in the chronic immunomodulatory setting are generally tailored to the patient's needs. The open-label, uncontrolled nature of the two studies inherently did raise concerns regarding the robustness of the efficacy data submitted. Also there were uncertainties regarding the MRC score system used by the applicant and the clinical relevance of the results obtained. However, the applicant has provided supplemental data on (i) dynamometry of large muscle groups and (ii) grip strength in response to treatment. These data did mitigate these uncertainties leading to the conclusion that the limited data are reasonable re-assuring.

There is lack of knowledge of the long-term use of KIOVIG in the management of multifocal motor neuropathy (beyond the timescale of the currently submitted trials) and whether or not muscle weakness may remain improved or continue to weaken in spite of treatment. There is lack of knowledge on whether or not use of KIOVIG would prevent involvement of motor nerves not yet affected. Furthermore, there is lack of knowledge on the overall impact of KIOVIG on the long-term quality of life and long-term survival. However, it may be expected that knowledge of the consequences of long-term use of KIOVIG may be gathered through surveillance during market exposure.

Overall, it is considered the available data for KIOVIG in MMN that is specifically generated for this product is limited; the data is supported by data from other IVIg preparations which was deemed acceptable. Overall, the available data is considered sufficient for granting the indication but this limitation has been reflected in the RMP as important missing information. Consequently, the CHMP considers the results of the randomized, placebo-controlled trial (Study 160604) currently ongoing in the US as relevant to corroborate the efficacy and safety of KIOVIG in the treatment of patients with MMN. The provision of the final CSR of this study is therefore requested as a condition to the marketing authorisation.

Risks

Unfavourable effects

The AE reported with KIOVIG in patients with MMN reflect what has been reported with KIOVIG in other indications. Side effects were reported in 35% of patients and included skin reactions, fatigue and – most commonly- headache. All events were classified as non-serious and were reversible. All AE reported with KIOVIG in MMN patients are already listed in the SmPC.

Therefore it is not expected that the use of KIOVIG for the treatment of MMN will have an altered safety profile.

Uncertainty in the knowledge about the unfavourable effects

The safety database from completed clinical trials with KIOVIG in MMN only covers 20 patients and is therefore relatively small. However, the data as provided with this application as well as what is known from other IVIgs in the treatment of MMN does not indicate a relevant change in the safety profile.

The limited clinical data regarding treatment in patients with MMN has been identified as important missing information in the RMP. Additional safety and efficacy data will be provided in the KIOVIG PSURs (reverted to 6 monthly cycle) as well as in the final CSR of the randomized, placebo-controlled study currently ongoing (Study 160604).

Balance

Importance of favourable and unfavourable effects

MMN is a rare, progressive debilitating disease that most commonly affects distal upper limb muscles. Though rarely fatal, the disease causes significant functional disability that interferes with daily activity such as independent eating, grooming, writing, opening and locking doors and holding objects. Any therapy to increase muscle strength and allow the patient to regain independence and resume a normal daily life is therefore essential.

In the last 10 years literature studies and case reports have repeatedly shown a benefit for the use of IVIgs in this condition. Generally, the response rate seen is around 75%; over time an increase in IVIg dose may become necessary to maintain the desired effect. This has now been confirmed by a "patchwork" approach of the company who submitted data with two forerunner products (Endobulin, GAMMAGARD) and their current product (KIOVIG) in initiation and maintenance settings, a comprehensive analysis of the literature, and of the feasibility of extrapolation between products.

Alternative treatment options are limited. Patients with MMN rarely respond to treatment with steroids and plasma exchange and may even worsen. Mycophenolate mofetil is ineffective. Very limited data are available showing a weak positive effect of interferon and natalizumab, and a more positive effect with rituximab. Cyclophosphamide appears to be the most effective treatment apart from IVIg. However, long-term treatment with cyclophosphamide is restricted due to its safety profile and high toxicity.

Given that this is a chronic, progressive disease that affects young adults and that there is not any suitable, alternate treatment then the increased muscle strength and lessened disability with associated improved quality of life in response to KIOVIG is considered to be important from the clinical perspective. Moreover, since there is not at present an IVIg that is licensed across Europe for management of multifocal motor neuropathy then this would be considered to be a product that addresses an unmet medical need.

There are no high toxicity risks related to the use of IVIgs. In general they are well tolerated even if given life-long as e.g. in replacement therapy. Risks such as hypersensitivity reactions, aseptic meningitis, thromboembolic events, or renal failure are grave but rare and risk minimisation efforts are undertaken by the company to address these side-effects. The unfavourable effects of skin reaction, fatigue and headache have been well described and documented for KIOVIG in its use for other indications and would not be considered to detract from the favourable effects.

Benefit-risk balance

It is considered that the increased muscle strength in response to KIOVIG treatment of multifocal motor neuropathy and the potential for this increase to persist over time with associated improved quality of life outweigh both the negative impact of adverse effects, as described, and the inconvenience of needing to administer an intravenous preparation.

Discussion on the benefit-risk assessment

There remain uncertainties in the full impact of treatment muscle weakness of multifocal motor neuropathy with KIOVIG: it is anticipated that these uncertainties may be addressed by the ongoing randomised, controlled study being conducted in the USA.

There is uncertainty in the ability of KIOVIG to maintain increased muscle strength over time. Progressive weakness in any one subject would lead to a shift in the benefit-risk balance for that subject with further treatment being considered to be futile. Since subjects receiving KIOVIG for management of multifocal motor neuropathy will be under continuing physician management and review then it may be expected that the development of lack of response in any one subject to KIOVIG will be addressed promptly. Overall, however, it is considered that the MAH has provided acceptable data to support the application for the use of KIOVIG in the indication for multifocal motor neuropathy. Against this background, the CHMP considered that the benefit-risk-profile for KIOVIG is positive for the treatment of multifocal motor neuropathy and that the current variation application is approvable.

3.15. Levemir

In support of the extension of indication 2 clinical studies were submitted.

The already completed Trial NN304-1689 and ongoing extension Trial NN304-1690 at submission were agreed on, during the paediatric investigation procedure by the PDCO. The SA, provided in 2005 by the CHMP, was not followed completely. As agreed on during the PIP procedure three additional studies, including NN1250-3561, will cover the currently missing data regarding PK-data in small children and nocturnal hypoglycaemia data in children using CGM devices.

The data that were collected in the studies from the whole 2-year treatment period suggest that insulin detemir is safe and efficacious and can be used in children between 2 and 16 years of age.

In the basal-bolus treatment regimen, the efficacy and safety of insulin detemir was compared to NPH insulin when both were used once or twice daily according to pre-trial regimen, in combination with insulin aspart as mealtime insulin. Insulin detemir was as safe and efficacious as NPH insulin in treatment of children and adolescents from 2-16 years with type 1 diabetes mellitus. Children treated with insulin detemir had less hypoglycaemia, less weight gain and fewer SAEs than children treated with NPH insulin.

Potential benefits that may be expected from the use of insulin detemir compared with NPH insulin in young children (2-5 years) are related to a lower within-subject variation in fasting plasma glucose, less hypoglycaemia (both 24h and nocturnal hypoglycaemia, which was not off-set by an increase in diurnal episodes) and less inappropriate weight gain. The overall AE profile for young children was similar to that of NPH insulin.

Obtaining good glycaemic control is a challenge for children and adolescents, due to growth, variable lifestyle, hormonal changes, and the need of assistance with insulin injection. The titration of insulin doses to obtain the target plasma glucose values led to similar HbA1c and fasting plasma glucose values with similar insulin doses per kg body weight in the two treatment groups. The ratio of insulin detemir/NPH insulin mean daily insulin doses at end of trial was close to 1 for both basal and bolus insulin, meaning that mean doses were similar in the two treatment groups. For the insulin detemir treated subjects continuing treatment for the complete 2-year period mean HbA1c levels were relatively stable, with a slight increase over time (mean HbA1c for all subjects at baseline was 8.43% and at end of trial 8.74%). Throughout the 2-year period, mean HbA1c was lowest for the young

children and highest for the adolescents. Overall, children in the 2-5 years of age group maintained better glycaemic control, compared to the older children.

The increase in HbA1c seen in both treatment groups may, as suggested by the MAH, reflect the general difficulties in treating children for whom many factors, including: fear of hypoglycaemia, social status, different country distribution, available help in day care or school and highly variable lifestyle, influence the glycaemic control. It might be speculated whether the titration of the insulin doses was sufficient or whether further intensification of the insulin treatment was hindered by hypoglycaemia or fear of, especially nocturnal, hypoglycaemia.

The observed changes in the insulin antibodies of children with type 1 diabetes treated with insulin detemir in a basal-bolus regimen with insulin aspart as mealtime insulin over two years do not seem to present a safety concern. The estimated antibody profile based on data from the whole 2-year treatment period showed that after an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level.

In conclusion, although the number of children 2-5 years of age exposed to detemir was only 41 the data from Trial NN304-1689 and NN304-1690 support the extension of the current indication for insulin detemir to include the use of insulin detemir in children 2-5 years. The number was in agreement with the agreed Paediatric Investigation Plan saying: "In the insulin detemir group, at least 40 between 2 and 5 years …. at randomisation". These young children, irrespective of gender, did as well as the older children ≥ 6 years for whom insulin detemir was approved in EU in 2005. Insulin detemir was as safe and efficacious as NPH insulin in treatment of children and adolescents from 2-16 years with diabetes mellitus. Children treated with insulin detemir had similar glycaemic control, less hypoglycaemia, few severe nocturnal hypoglycaemia episodes, less weight gain and fewer serious adverse events than children treated with NPH insulin. The longer duration of action, the lower within-subject variation in fasting blood glucose, the lower risk of hypoglycaemia and the lower body weight gain of s.c. insulin detemir compared to NPH insulin may offer advantages for the treatment of young children with diabetes mellitus. The proposed indication for Levemir use is children aged 2-5 years is therefore considered as approvable.

3.16. Lucentis

Benefits

Demonstrated benefits

The mechanism of action of ranibizumab is to decrease permeability of leaking blood vessels. This mechanism of action is valid independent on whether targeting retinal vessels in RVO, DME or the choroidal vessels in AMD. Therefore, available data from the AMD- and DME-populations adds to the basic understanding of the drug. This is of relevance also for understanding the treatment of RVO.

BRVO

A convincing outcome has been demonstrated, both with regards to effect size and statistical significance. After 6 months treatment, subjects with BRVO treated with 0.5 mg ranibizumab gained in average 18 letters in VA compared to 7 letters for sham-treated subjects (primary endpoint, $p<0.0001$). After the first 6 months of the study, previously sham-treated subjects received 0.5 mg ranibizumab for an additional 6 months (masking maintained), while subjects previously treated with 0.3 or 0.5 mg ranibizumab continued on their originally assigned treatment. At month 12, previously sham-treated subjects had gained 12 letters (95% CI 9.6, 14.6) vs. 18 letters in the 0.5 mg ranibizumab-treatment group (95% CI 15.8, 20.9). At month 6, also a substantial proportion of

ranibizumab-treated (0.5 mg) subjects gained ≥ 15 letters in VA; 61 % vs. 29 % in the sham group ($p<0.0001$). The outcomes of the key analyses were supported by sensitivity analyses. As for the primary endpoint, the switch to active therapy during the 2nd part of the study increased the proportion of responders in the previous sham-group, but the numerical advantage for subjects that had received ranibizumab during the whole study remained. The 0.3 mg dose of ranibizumab was also highly effective, but numerically inferior to the higher dose in the VA-based analyses. Other secondary and exploratory endpoints (based on VA or anatomical measures) were consistently in favour of ranibizumab-treatment.

During the extension part of the study, the effects on VA were essentially maintained or increased slightly. At 24 months, the VA outcome in the treatment group that initially received sham-injections was very similar to the outcome in patients that received ranibizumab from study start. These figures may thus indicate that it is not necessary to initiate treatment immediately. However, the rapid improvement in VA upon treatment initiation (5-6 letters over sham after 1 week, $p< 0.0001$) is recognised as a benefit for the patient.

However, the design of the BRVO study has limitations and deviates from recommendations given in the CHMP-advice. Although positive effects on vision after laser photocoagulation are not expected in the short term, laser photocoagulation has been shown to be of long-term benefit for subjects with BRVO. Since subjects in the sham arm were deferred (3 months) laser rescue, the test agent has consequently a 3-month advance start over laser. Further, in BRVO, spontaneous improvement in VA is not uncommon and subjects may continue to improve during the first year. Thus, the 6-months sham-controlled phase of the study limits the possibility to assess the impact of a spontaneous improvement in BRVO vs. the magnitude of (contribution of) effect of ranibizumab, this since the results for the treatment groups include besides the outcome of the spontaneous resolution of the oedema also effects of delayed laser. On the other hand, masking was maintained over the 12 months and so was the controlled design of the study (the originally randomised groups were still compared to each others) and as detailed below, it is clear that there is an additive effect of ranibizumab and that this effect is rapid and substantial. However, the study design does not allow assessing the exact magnitude of effect of ranibizumab.

In subgroup analyses, by visit at which the first laser treatment (month 3, 4, 9 and never) was administered, all ranibizumab-treated groups showed, on average, an improvement in VA before receiving their first laser treatment. Even though this subgroup analysis is driven by the outcome (subjects who did worse received laser treatment), the observation that sham-treated subjects that did not require laser had, on average, an ~ 6 letter gain in mean BCVA at Month 3 compared to the mean ~15 letter gain seen in the corresponding non-laser 0.5 mg group at Month 3 supports a relevant treatment effect of ranibizumab. Additionally, the extent of the need for laser rescue (almost three-fold more in the sham-group compared to ranibizumab) is supportive of a treatment effect of ranibizumab.

Additionally, in the recent SCORE study (Arch Ophthalmol, 2009), 29% of laser-treated BRVO-subjects gained ~15 letters of VA after 12 months. This is very similar to the 6 months data in the sham group (29%) in the current study and to be compared with the ~60% of 0.5 mg ranibizumab-treated subjects that gained ≥ 15 letters of VA (month 6 and 12). Taken together, it is clear that ranibizumab has an additional treatment effect also in BRVO and the subgroup analyses as well as published data indicate that this effect size is of clinical relevance.

Although ranibizumab had a 3-month advance start over laser, deferral of laser for 3-6 months is according to clinical practice and an effect of laser on VA is expected to be seen after a number of years. Since the majority of subjects (65%) had a duration of BRVO of less than 3 months, it is reassuring that the subgroup analysis of subjects that will not be treated with laser in clinical practice

(i.e. < 3 months duration of BRVO) demonstrated a convincing effect of ranibizumab (9-11 letters over sham).

Overall, the effect of ranibizumab has been demonstrated also taking the spontaneous improvement and the 3-month deferral of laser into account. Thus, the lack of data evaluating the exact magnitude of the additive effect of ranibizumab is of minor concern.

CRVO

The design of this study also deviates from the CHMP advice since the sham-controlled period was not maintained over 12 months. As for BRVO, the masked and controlled design of the study was maintained (the originally randomised groups are still compared to each others) and the presented study is considered acceptable since no overall spontaneous improvement will be expected in this group of patients. In CRVO, ranibizumab-treated subjects (0.5 mg) gained in average 15 letters vs. 1 letter in the sham group ($p<0.0001$). As in the BRVO-study, after the first 6 months of the study, sham-treated subjects received active treatment. At month 12, previously sham-treated subjects had gained 7 letters (95% CI 4.5, 10.0) vs. 14 letters in the 0.5 mg ranibizumab-treatment group (95% CI 11.5, 16.4). Also in CRVO, a substantial proportion of ranibizumab-treated (0.5 mg) subjects gained ≥ 15 letters in VA; 48 % vs. 17 % in the sham group ($p<0.0001$). The outcomes of the key analyses were supported by sensitivity analyses and the secondary and exploratory endpoints were consistently in favour of ranibizumab-treatment. Overall, the outcome in subjects with CRVO is considered impressive. The effect was also maintained during the extension study with a slight drop in VA between month 12-15 (time for the first scheduled visit), where after VA remained stable. At 24 months, subjects that were previously sham-treated did not gain as much VA as those who were treated with ranibizumab from study start ending up with a difference of almost 10 letters in mean VA.

BRVO and CRVO

With preliminary data from the extension study, it has been confirmed that the treatment effect is maintained, at least over one additional year.

Neovascular iris complications, especially in CRVO, are serious and if left untreated, they almost always lead to increased IOP and secondary glaucoma. Importantly, the incidence of iris neovascularisation was numerically smaller (few subjects in total) in ranibizumab-treated subjects compared to those who were sham-treated during the first 6 sham-controlled months of the core studies. However, at 12 months, a slightly increased incidence was observed and even though few subjects developed these complications during the extension study and the MAH has committed to further address neovascular complications in the planned studies E2401 and E2402 as well as in the LUMINOUS study.

The treatment effect was consistent over subgroups, including the group of RVO patients with diabetes which is of importance since diabetes is a major risk factor for RVO. The majority of subjects had a duration of RVO of less than 3 months (BRVO 65%, CRVO 69%). However, a treatment effect was shown also in subjects with a longer duration of RVO. Although very small subgroups, it is also reassuring that subjects with retinal ischaemia seemed to have benefit of treatment, however, the limited experience in these subjects is now addressed in the SPC, section 4.4 and will be further investigated in upcoming studies.

During the extension period, subjects received in average 3 additional injections but the variability was large (range 0-11). Further, in BRVO, approximately 40% of subjects remained with a stable VA without any additional injections while the corresponding figures in CRVO were 20%. Thus, the analyses of the, in total, 2-year data confirm the large variability in both subsets of RVO and also that there is a potential to withdraw treatment in some patients. The MAH intends to further address whether there is a potential to adapt the monitoring frequency to individual needs by assessing the

predictive value of observed responses to treatment and for treatment interruption in the upcoming studies E2401 and E2402 (as well as in LUMINOUS). If appropriate, the outcome of the studies could be used to suggest new treatment recommendations. This approach was endorsed by the CHMP.

Uncertainty in the knowledge about the beneficial effects

Although it is considered that a clinically relevant effect of ranibizumab in subjects with BRVO has been sufficiently demonstrated, the submitted data does not address whether there is a sustained advantage of ranibizumab therapy over standard care in the long-term.

Even though data are reassuring, very few subjects with retinal ischaemia and a long duration (>12 months) of RVO were included in the studies, and some uncertainties with regards to the benefit in these groups remain. In the preliminary data from the extension study HORIZON, the rate of retinal ischaemia raised no new concerns. However, whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab remains unknown, and the currently available data only give limited assurance. Information on the limited experience in these subjects is now given in the SPC. However, information not to treat patients with signs of functional loss due to ischaemia is also warranted. In addition, it is considered of high importance that the MAH will make efforts to characterise the benefits of ranibizumab-treatment in the RVO population with ischaemic disease and the planned studies are acknowledged.

Risks

Demonstrated risks

Ranibizumab is given by IVT injections. The risks with such injections are characterised from the previous development programme including patients with AMD and DME and consists mainly of increased IOP that is, in most cases, non-serious, transient and can be managed. In addition, there are risks for intraocular inflammation, damage to intraocular tissues including increased risks for retinal tears and detachment as well as potentially sight-threatening endophthalmitis. Overall, the submitted studies indicate that the risks appear similar for patients with RVO and there were no significant new safety signals. Concomitant laser rescue and ranibizumab treatment did not appear to increase the incidence and severity of adverse events. Additionally, during the extension study (i.e. in subjects exposed to ranibizumab for a mean total of 2.2 years) ocular AEs were largely comparable with those previously reported. Although the incidence of retinal depigmentation or pigmentation and cystoid macular oedema increased with time, they were likely to be manifestations associated with the disease.

With regards to non-ocular AEs, as in the previously studied populations, the majority in this fairly representative population was mild to moderate in severity and few were suspected to study drug and/or ocular injection. An increased number of subjects experienced cardiac heart failure congestive and TIA (SAEs) compared to the first treatment year. However, in view of the significant co-morbidities (confirmed by disease history), the figures (including those regarding ATEs) are not considered alarming and are continuously monitored. The current information in section 4.4 and 4.8 of the SPC regarding risks with systemic VEGF-inhibition is relevant also for this group of patients.

The safety data set in RVO consists in total of 525 subjects treated with ranibizumab for up to one year and 413 subjects that have been treated in total for a mean of 2.2 years. Of these, 269 subjects have been treated for ≥ 2 years (occasional subjects up to 3 years). However the overall experience of IVT Lucentis in ocular disease has become quite large with exposures of ranibizumab in 3736 and 337 patients with AMD and DME, respectively and additional safety data will be generated in the registry study LUMINOUS as well as in the upcoming phase IIIb studies (studies E2401, E2402).

Uncertainty in the knowledge about the unfavourable effects

A remaining concern is the potential effect of ranibizumab on retinal ischemia. During the sham-controlled phase of the study (6-months), more untreated patients developed retinal ischaemia, while during the 12 months, there was a tendency towards an increased number of patients with ischaemia of varying severity compared to baseline. At month 24, 6 % of BRVO- and 12 % and CRVO-patients that were non-ischaemic at baseline developed ischaemia. However, development of retinal ischaemia is part of the disease, e.g. there are reports that in subjects with CRVO, 8 to 34 % of non-ischaemic subjects convert to an ischaemic state over a number of years and the rate of conversion presented appears not to be alarming. Still, it remains unknown whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab and the currently available data only give limited assurance. The MAH has committed to further address this concern in the upcoming phase IIIb studies and in LUMINOUS as well as to follow this as detailed in the RMP.

There were occasional subjects experiencing a second event of RVO. As for retinal ischaemia, it is not known whether anti-VEGF therapy may increase the risk for recurrences of RVO even though the rate of recurrences was not alarming compared with the published rates. Although included in the RMP (covered by search terms), this should be further addressed in future studies.

With respect to the increased incidence of macular oedema observed during the extension period, the MAH has justified it as related to suboptimal monitoring and/or treatment. These differences have also been observed when macular oedema was reported as serious events. However, a potential relevant adverse event cannot be discarded. The post-approval planned studies should thus also address this potential issue.

The RVO is also a population with a high prevalence of glaucoma and IOP may be more closely monitored in ranibizumab-treated subjects with RVO. The MAH-proposed amendment of the SPC section 4.4 to include not only transient increases of IOP, but also to address that such sustained increases are considered of high relevance for the various Lucentis patient populations. The CHMP considered this to be acceptable.

Balance

Importance of favourable and unfavourable effects

Treatment with ranibizumab resulted in a clinically convincing and a statistically significant improvement of VA in subjects with RVO. However, the outcome of the non sham-controlled 6-months phase of the BRVO-study includes the outcome of the spontaneous resolution of the oedema as well as the effect of the delayed laser rescue. Although the exact effect size of ranibizumab cannot be concluded on, the subgroup analyses as well as published data support a clinically relevant magnitude of effect of ranibizumab that cannot be explained by a spontaneous improvement or the deferred rescue laser. The rapid onset of improvement of VA in ranibizumab-treated subjects with BRVO is also acknowledged and of value for the patient. In view of the poor prognosis in CRVO, the outcome in this subset of RVO considered compelling.

Treatment is not without risks; however the risks appear comparable to that previously identified in the AMD- and DME-populations. Besides risks for the manageable increase in IOP and injection-related damage to intraocular tissues, rare, but important and potentially sight threatening risks are those associated with retinal detachment and endophthalmitis. The most important potential, although not frequent, non-ocular risks in RVO-patients that already have major cardiovascular risk factors are those that are previously identified, i.e. risks that may be related to systemic VEGF-inhibition.

Benefit-risk balance

The natural progression of BRVO is very variable. Published data indicate that if untreated, one third to three quarters of patients may improve their VA over 2-3 years, but a limited proportion of subjects gain ≥ 10 letters of VA (<20% year1 to <40% year 3) a significant proportion (>20%) of subjects end up with a poor VA (<20/200) after 3 years. If treated with laser, there are no major short-term benefits with regards to an improved vision (proportion with a ≥10 letter gain year 1 ~35%), however, over 3 years, 65% gain ≥ 10 letters in VA although ≥10 % of subjects have a VA ≤20/200 (BVOS, 1984). The current study presented a ≥ 15 letter gain in 61 % of patients after 6 months and 4% with a VA≤20/200 at 12 months. Although the long-term effects of ranibizumab-treatment are not characterised, the rapid improvement (that was sustained over 12 months) in VA is considered to be of high importance. In comparison with laser photocoagulation, the risk profile in ranibizumab-treated patients appears very different, and the immediate risk is estimated to be higher due to the IVT injection. However, laser photocoagulation destroys retinal vessels and causes scar tissue.

In CRVO, few patients gain significant VA, and with time severe vision loss is often developed. Laser treatment has not been shown to improve VA in CRVO, but during the last decade, a number of treatments have been investigated. Such treatments include vitrectomy and radial optic neurotomy (i.e. surgical procedures are associated with variable outcomes and not without major risks). With Lucentis, ocular drug-related AEs have been reasonably characterised, are manageable, but the potential risks regarding systemic effects of VEGF-inhibition remain. Also in CRVO, the effect of Lucentis on VA was maintained during the second year of treatment.

Recently, Ozurdex (dexamethasone implant) was approved to treat both subsets of RVO. Although no comparative data are available, 20-45% of subjects treated with Ozurdex increased their VA with ≥ 15 letters with no major differences between patients with BRVO and CRVO (EPAR).

The proposed posology for Lucentis in RVO is identical with that agreed upon for the treatment of DME (reason why the two posologies have been merged in the SPC) and supported since clear criteria when treatment is no longer recommended has been outlined in section 4.2 of the SPC. In addition, while in subjects with BRVO, laser treatment is usually withheld for a number of months to allow time for a spontaneous resolution of the oedema, the MAH further elaborated on when to initiate ranibizumab-treatment in these subjects. The MAH presented data that support an additional treatment effect of ranibizumab over sham also in subjects with a very short duration of BRVO, i.e. in subjects that also recovered significantly (≥10 letters between screening and study start) prior to treatment initiation. On the other hand, the (in total) 24 month HORIZON outcome indicate that subjects that were initially sham-treated appeared to catch up with those who received ranibizumab from study start. The data thus suggest that there is no need to initiate treatment immediately and even if treatment is delayed with 6 months, the average long-term outcome in VA is not negatively affected. However, it is clear that the time to improvement in VA is significantly more rapid in case of an early initiation of treatment. Overall, an approach to leave the decision whether to initiate treatment immediately or whether to "wait and see" up to the discretion of the physician is supported. As a basis for such decision-making, section 5.1 of the SPC has been amended.

Overall, the rapid and substantial improvement in VA, taking the reassuring safety profile into account, is considered to outweigh the risk whether there is a sustained advantage of ranibizumab therapy over standard care in the long term in BRVO. In CRVO, the benefits of treatment also outweigh the risks.

Collection of further data

The MAH will further evaluate the efficacy and safety of ranibizumab treatment in patients with visual impairment due to macular oedema secondary to RVO in the LUMINOUS study and in two additional, 24-month, Phase IIIb post-approval studies (CRFB002E2401 in CRVO and CRFB002E2402 in BRVO). These two studies are proposed to start Q4 2011.

In LUMINOUS, the safety reports will include all AEs, including the neovascularisation AEs. Interim reports will be submitted with PSURs, final evaluation within 9 months after end of the study.

In both Phase IIIb studies (E2401 and E2402) the MAH committed to the following:

- Efficacy evaluation of patients with or without retinal ischemia will include efficacy analyses in patient subgroups with different baseline ocular characteristics, including the presence or absence of retinal ischemia

- Safety evaluation of the retinal ischemia progression over time as well as adverse events in patients with or without presence of ischemia

- Safety evaluation of the neovascular complications based on the incidence rates of adverse events of ocular neovascularisation (cornea, iris, choroidal, retinal) - Patients with visual impairment due to macular oedema secondary to RVO will be included without limits of time since diagnosis of RVO

- In the second year, the study design will allow skipping a visit based on the VA stability criterion to evaluate the less frequent monitoring and further evaluate the rate of treatment withdrawal long term Study E2402 will further evaluate the added benefit of laser standard of care treatment in patients with BRVO. Both E2401 and E2402 protocols will be submitted within 1 month after approval.

The strategy for studies E2401 and E2402 is endorsed. In addition, the MAH may consider differentiating between ischaemic and non-ischaemic subtypes of RVO while applying additional the methodologies, e.g. some of those used by Hayreh and co-workers (2011). The MAH may also consider not excluding subjects with DR (including DME) and RVO in the upcoming studies E2401 and E2402 as well as preparing for analysis of those in the LUMINOUS study.

Conclusion

Based on the CHMP review of the data on efficacy and safety, the CHMP considers that the overall B/R of Lucentis in the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion is positive.

3.17. Ozurdex

Benefit

To support the extension of indication for Ozurdex in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, the MAH submitted a single phase III pivotal trial: An 8-Week, Multicenter, Masked, Randomized Trial (with an 18-Week Masked Extension) to Assess the Safety and Efficacy of 700 microgram and 350 microgram Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System Compared with Sham DEX PS DDS Applicator System in the Treatment of Non-Infectious Ocular Inflammation of the Posterior Segment in Patients with Intermediate or Posterior Uveitis. Assessment of efficacy and safety of Ozurdex in the treatment of non-infectious uveitis was based on this pivotal study, with safety data from the retinal vein occlusion and macular oedema studies being considered supportive. The initial concerns regarding the number of amendments to the pivotal trial were resolved and the CHMP considered that they did not have a relevant impact on the study results.

The results of the phase III study demonstrated that the 700 microgram implant was efficacious in the treatment of uveitis of the posterior segment of the eye. Both the 700 microgram and 350 microgram implant groups were statistically significantly superior to the sham group in the ITT and PP populations

for the primary and secondary efficacy endpoints. The results for the 700 microgram group were numerically superior to the 350 microgram group on most endpoints, but this comparison was not statistically siginificant.

Uncertainties about the benefit

The CHMP noted that according to the data in severe patients and the known course of the disease in many instances, re-dosing of Ozurdex would be reasonably expected in severe cases of uveitis. It was observed that efficacy appears to decrease after around 6 months and therefore, patients may need re-implantation. In terms of efficacy, as Ozurdex is a corticosteroid treatment, it is expected that the efficacy observed with a second implant would be similar to the one observed with the first implant. Although data on re-implantation are not available for Ozurdex in uveitis patients, in the RVO studies where patients entered a second open label extension after 6 months, patients achieved a similar treatment benefit to that of the first. Given that in both conditions the inflammatory process has a common mechanism, a second injection in uveitis patients was considered to have a similar effect to RVO patients.

Risks

The adverse event profile for Ozurdex in the treatment of patients with posterior uveitis was in line with that seen in the RVO studies.

The most frequently reported ocular adverse events were IOP increased, conjunctival haemorrhage, eye pain, iridocyclitis, uveitis, ocular discomfort and cataract, being all except for eye pain and uveitis more commonly reported in DEX 700 as compared to sham. In general, comparing the two tested doses, DEX 350 showed a slightly more favourable safety profile, with a lower incidence of the most frequently reported adverse events, than the high dose (DEX 700). On the other hand, a lower incidence of visual acuity reduced and macular oedema AEs, common complications of uveitis, were seen in DEX 700 compared to DEX 350 and Sham.

Uncertainties about the risks

The uncertainty regarding repeated use of Ozurdex was also discussed in terms of limited safety data. The CHMP noted that only six-month safety data are available in patients with posterior uveitis. The long-term safety data provided were based on the studies presented to support the currently authorised indication, i.e. macular oedema following RVO, and on the ongoing studies in diabetic macular oedema. The CHMP considered that the safety profile of repeated steroid use is likely to be consistent across the uveitis, RVO and DME indications, as each condition contains an element of inflammation. As described above in section 4.4.6, the safety profile from the six month study in uveitis was, with the exception of cataracts and conjunctival haemorrhage, in line with that of the RVO studies. Overall, the data presented by the MAH were considered relevant to support a positive benefit risk balance of Ozurdex in the uveitis patients.

As a high percentage of patients may require a second implant (64% of patients with non-infectious intermediate uveitis and 67% with posterior uveitis were classified as quiescent (Nguyen et al, 2011), it was considered relevant to further monitor the long-term safety profile in patients requiring more than 1 implant. In particular, the CHMP considered that the AEs most commonly reported during the first six months (e.g. increased IOP, cataract, conjunctival haemorrhage) should be analysed within repeated administration of Ozurdex in the post-marketing setting. As the MAH is planning a long-term safety/repeat dosing study of Ozurdex in patients with RVO the CHMP requested that at least a subgroup of patients with uveitis be included.

The CHMP also discussed the most suitable dose in less severely affected patients, who would be nonetheless candidates for intravitreal treatment, and asked the MAH for a justification of the 700 microgram dose. The MAH concluded that both doses were shown to be safe and effective in patients with baseline VH scores of +1.5 or 2; nevertheless, the response to the 700 microgram dose was numerically superior in efficacy across a broad range of endpoints and at almost all timepoints, had an earlier onset and longer duration of action and no significant difference in overall safety profile was observed between the two doses. Furthermore the incidence of adverse events such as cataracts and increased IOP which would be expected to increase with increasing corticosteroid dose was not significantly different between the two doses. In this context, the MAH chose to apply only for the higher dose. The CHMP considered that the risk benefit balance was sufficiently substantiated with the current data and that it is positive for the 700 microgram dose in the proposed indication.

Conclusion

Overall, the CHMP concluded on a positive benefit-risk balance for the 700 microgram dose in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

3.18. Onglyza

Benefits

Beneficial effects

The efficacy and safety of the addition of saxagliptin to insulin was investigated in one clinical study (057). This was a randomised, double-blind, placebo controlled trial in 455 patients, insufficiently controlled by insulin or insulin plus metformin. After screening and lead-in, patients were randomised in a 2:1 ratio to receive saxagliptin 5 mg qd or placebo for 24 weeks.

The addition of saxagliptin to patients treated with insulin resulted in a decrease of HbA1c. The maximum was reached at week 12 and was maintained trough week 24. The mean placebo corrected decrease was -0.41%. Secondary endpoints were in line with this result. Results were similar in subjects with and without metformin use at baseline.

Mean total insulin dose increased from baseline to week 24 in both groups. However, the mean increase was lower in the saxagliptin group (1.7 units) than in the placebo group (5.0 units). After this short term period, patients entered a long-term phase of 28 weeks, the data of which had been provided by the applicant during the evaluation and did not show any additional efficacy aspects; the observed decrease of HbA1c in particular was sustained thought week 52.

Overall, both primary and secondary parameters indicate that the addition of saxagliptin to patients treated with insulin was effective. The effect was modest with an HbA1c adjusted mean difference from placebo of -0.41% but the study demonstrated nevertheless a statistically significant reduction, and the effect size in this population with advanced T2DM was still considered to be of clinical relevance by the CHMP.

Uncertainty in the knowledge about the beneficial effects

In both groups a relative large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).

The placebo group had a considerable reduction in HbA1c of 0.32%, likely attributable to dietary and exercise factors, some of which may have extended beyond randomisation.

There were differences in effect according to geographic region. The adjusted mean change in HbA1c from baseline was -0.69% in Europe, -0.64% in North America, -1.15% in Latin America, and -0.58% in Asia. The response in the placebo group was -0.41% in Europe, -0.15% in North America, -0.52% in

Latin America and 0.06% in Asia. This resulted in a difference from control of -0.29% in Europe, vs -0.49% in North America, -0.63% in Latin America and -0.64% in Asia. However, there was no evidence of a treatment-by-region interaction (p=0.262) and a difference in placebo-corrected response between Asian and European patients had previously also been observed with another DPP-4 inhibitor.

Risks

Unfavourable effects

In general saxagliptin was well tolerated. There were no unexpected or new adverse events.

The overall incidence of AEs during the short-term treatment period (prior to rescue), excluding all events of hypoglycaemia, was 52.3% in subjects receiving saxagliptin compared with 55.6% in subjects receiving placebo. In the saxagliptin group the 3 most common events were urinary tract infection, upper respiratory tract infection, and headache whereas in the placebo group the 3 most common events were influenza, urinary tract infection, and pain in extremity.

Patients on saxagliptin had no more hypoglycaemia than placebo treated patients.

Data submitted during the evaluation for the extension period through week 52 of study 057 did not show any different findings compared to the short term period.

Uncertainty in the knowledge about the unfavourable effects

There was one death due to myocardial infarction and two other cardiovascular-related SAEs in the saxagliptin group, all considered unrelated to study medication. Patients had already a cardiovascular history and/or hypercholesterolemia. Nevertheless, cardiac safety is specifically monitored in 6-monthly periodic safety update reports and further addressed in the context of a cardiovascular outcome study performed by the MAH.

Balance

Importance of favourable and unfavourable effects

The addition of saxagliptin resulted in a decrease in HbA1c for the whole population.

However, in both groups a relative large percentage of patients discontinued because of lack of glycaemic control (22.7% vs 32.8 in the saxagliptin and placebo group, respectively).

There were no differences in the size of the effect between races, but there were differences between geographic regions. These were mainly due to differences in placebo-response, with no response in Asian people and a decrease of HbA1C of -0.41% in European patients. This resulted in a relatively small placebo-corrected numerical decrease of -0.29% in the European population of the study. In this heavily treated population with advanced diabetes the effect size was nevertheless still considered to be clinically relevant by the CHMP.

Saxagliptin was in general well tolerated, with no unexpected findings, and no more side effects than the placebo treated patients. Although the three cardiac adverse events were serious, their relation with saxagliptin, if any, is not established. Therefore, cardiovascular adverse events are being closely monitored and further addressed in a dedicated outcome study.

Benefit-risk balance

The effect of adding saxagliptin on HbA1c was modest, especially in European patients, however was still considered to be relevant for the patient group involved. Treatment was not associated with an increase in events of hypoglycaemia, and the increase of daily insulin dose was slightly less in the saxagliptin group. Saxagliptin was well tolerated.

Discussion on the benefit-risk assessment

Saxagliptin, when added to an existing insulin treatment, resulted in further reductions of HbA1c, without showing any unexpected consequences in its safety profile.

The overall B/R of saxagliptin added to insulin is positive.

3.19. Pradaxa

Benefits

- Beneficial effects

The pivotal trial, RELY (1160.26), compared dabigatran with the current standard warfarin for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation. A relevant patient population including patients with considerable cardiovascular comorbidities, advanced age, reduced renal function, stroke risk profiles, and concurrent medications has been enrolled. In contrast to recent AF trials (SORTIF III and IV, ACTIVE-W, AMADEUS) patients were balanced as regards their previous VKA use. Superiority of DE150 bid vs. warfarin was demonstrated for the primary endpoint "time to first occurrence of stroke/SEE", and non-inferiority was demonstrated for DE110 bid vs. warfarin. The Kaplan Meier curves suggest that the effect is consistent over time. The primary endpoint was driven by strokes; systemic embolisms (SSE) were very rare in all treatment groups. Approximately half of all strokes were disabling, with no significant differences between treatment groups. Haemorrhagic strokes and intracranial haemorrhages (ICH), though overall rare, were considerably reduced for either dose of dabigatran compared to warfarin. The benefit of both dabigatran dosages vs. warfarin on ICH was remarkably consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA). Also for the secondary endpoints, the composites of "stroke, SEE and all cause death", as well as "stroke, SEE, PE, MI and vascular death" DE150 bid was superior to warfarin. As described below, some of the components of the latter composite were, however, in favour of warfarin. Not unexpectedly, the quality of warfarin treatment as expressed by the time in therapeutic range (TTR) influences the comparisons between dabigatran and warfarin. The outcome of warfarin treatment improved with increasing TTR and the presented analyses clearly demonstrated that the benefits observed in the comparison of dabigatran to warfarin diminished if INR control was good with TTR >70%. This was reflected in Section 5.1 of the SmPC. Still, for the overall population as well as for patients ≥ 75 years of age DE150 bid appeared more attractive with respect to the primary endpoint (prevention of stroke/SEE) when compared to warfarin at centres with TTR $\geq$70%. DE110 bid appeared comparable to warfarin in this case.

Choice of dabigatran dosages: Two DE dosages of 110 mg bid and 150 mg bid have been proposed by the MAH for this extension of indication. The overall results demonstrated an overall positive benefit for both dosages on the primary composite efficacy endpoint (stroke/systemic embolism) and safety (decrease or similar overall bleedings) compared to warfarin. Age factor is of paramount importance as in real life, elderly patients will certainly constitute the main target population of non valvular AF patients. Despite higher bleeding rates on DE in elderly ≥ 75 years, DE110 bid should not be systematically recommended to patients between 75-80 years as the effect of DE110 bid on stroke/SEE is lower than DE150 bid (but still favourable vs. warfarin). Thus, for patients ≥75 years of age 68 MBE and 3 ICH (out of 10000 patients) would be avoided with DE110, but 46 additional strokes/SEEs would be experienced compared with DE150. It was concluded that DE110 bid can be individually envisaged in at risk patients, since the bleeding rates are decreased with this dosage in patients ≥ 75 years. In contrast for patients ≥ 80 years, DE110 bid seems to be the appropriate dose: ten additional stroke/SEE would be experienced however 99 MBE and 37 ICH would be avoided with DE110 bid compared to DE150 bid. Data for the elderly ≥ 85 years are more limited. With DE110 bid 53 more stroke/SEE would be observed but 128 MBE and 63 ICH would be avoided as compared to DE150 bid. Though the overall death rates were higher in very elderly treated with dabigatran as compared to warfarin (DE110 bid: 11.13%; DE150 bid: 9.25%; warfarin: 7.95%) the frequency of vascular death was similar between the 3 groups (DE110 bid: 5.33%; DE 150 bid: 4.73%; warfarin: 4.64%). The rates of overall death should also been seen in the context of the benefit of DE 110bid on often debilitating strokes and ICH in these very elderly patients.

Despite slightly higher exposure of DE in patients with moderate renal impairment, low body weight or patients of female gender no dose reduction is considered necessary for the overall population.

The risk of major bleeds was significantly lower for DE110 bid treated patients vs. patients treated with warfarin (HR 0.80 (95% CI: 0.70, 0.93; p=0.0026)). No significant difference was observed for DE 150bid treated patients (HR 0.93 (95% CI: 0.81, 1.07; p=0.3146)). Nonetheless, subgroup analyses showed, that patients <75 years of age had a significantly lower risk of major bleedings with either dose of DE compared to warfarin (results on MBEs are based on analyses including outcome events identified after data base lock). The risk of life-threatening bleedings and ICH were statistically significantly reduced for either dose of DE compared to warfarin. Despite low absolute numbers of ICH, the benefit of both dabigatran dosages vs. warfarin was remarkably consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA).

The lack of need for dose adjustments and monitoring during treatment with dabigatran is regarded as a benefit vs. warfarin treatment. In addition to the lack of food interactions, dabigatran has a different interaction profile compared to warfarin, offering a treatment alternative based on patients' co-medication.

- Uncertainty in the knowledge about the beneficial effects.

Study design: In the RELY study, patients and investigators were not blinded to warfarin or dabigatran treatments. Blinding was only kept as regards the two doses of dabigatran treatment. It cannot be excluded that the unblinded study design may have influenced the outcomes of the study. Appropriate measures have been implemented to minimise bias but considering that all evidence rest on only one pivotal study, inspections of the sponsor, the CRO and of two sites (in USA and Greece) were conducted. Another reason for the inspections was some discrepancies found by the FDA in the database of the RELY study. The two critical findings at the sponsor's site were mainly due to lack of communication between sponsor and the CRO (which was the PHRI = Population Health Research Institute). The PHRI contract did not specify all the tasks transferred from the MAH. As a consequence the data quality was compromised. Excessive error rate on study critical data was identified by the FDA, in particular severe transcription errors for INR values transferred from CRFs to data listings.

Implementation of special measures were required to solve these data quality issues resulting in extensive re-checks on CRF accuracy, data plausibility and consistency checks (between the CRF and database). This has been done and this issue was regarded by the CHMP as resolved. While the study was conducted perfectly at the inspected US site, from a clinical point of view one critical and one major finding identified at the Greek investigator site 901 were considered of importance. Large gaps between two consecutive INR controls were identified in some patients despite protocol specified gaps of 4 weeks. In addition, INR transcription errors were identified in 5 patients out of 26 patients revised. These findings had the potential to disfavour warfarin vs. dabigatran due to potential reporting of embolic events in patients with INR values "out of therapeutic range" despite being reported in the study protocol as being in therapeutic range. In 6 of these 8 cases, the investigators placed the patients in therapeutic range despite being below therapeutic range. In the 2 additional cases, the INR was already within therapeutic range either in the source data or in the transcription. There were no cases of placing the INRs out of range despite being within therapeutic range. Hypothetically, INR measurements might be unreliable. It could be argued that this issue is critical in an unblinded study. However the identified Greek findings did not lead to dose-adjustments of warfarin treatment based on wrong INR values, the findings were thus not considered to influence the primary endpoint Stroke/SEE. In response to the D180 LoOIs the MAH provided clarification on the issue, and no additional inspections of other Greek or European sites or further questioning on this issue were deemed necessary. However, the CHMP concluded that the MAH had not adequately addressed the issue of INR transcription errors in patients on warfarin experiencing major events. Therefore, the MAH was requested to provide a review of the chain of INR transcriptions in all warfarin treated subjects who experienced thromboembolic events, myocardial infarction and intracranial haemorrhage. The MAH has thoroughly described the way of collecting source INR data collection and handling of source- and CRF INR data. Based on these descriptions the CHMP was of the opinion that there is no reason to believe that the errors have biased the results in favour of dabigatran.

For the proposed indication the target population and the pattern of use of dabigatran will completely change. The new indication will include a great majority of elderly patients, with prescriptions mainly made by general practioners or cardiologists outside of hospital environment, with a monitoring that could be softened with the time, due to the long-term duration of treatment. The safety consequences of these important changes have been sufficiently addressed by the MAH in the clinical program. Appropriate prescriber guides (one for both indications) and patient alert cards have been drafted. Also, a drug utilisation study and post-authorisation studies aiming to evaluate the effectiveness of the risk minimisation activities and to assess potential off-label use outside AF will be conducted as specified in the updated RMP and the LoU.

Risks

- Unfavourable effects

The limitation of effective anti-thrombotic therapy is increased risk of bleedings.

Age: Age was a significant factor for MBE. Whereas patients <75 years had a significantly lower risk of MBE with either dose of DE compared to warfarin , the risk for patients aged ≥ 75 years of a MBE was approximately similar for DE 110bid compared to warfarin (HR 1.01 (95% CI 0.83, 1.23) but was higher for DE 150bid vs. warfarin (HR1.18 (95% CI 0.98, 1.43)). Moreover, in very elderly patients > 85 years of age, an increased risk of MBEs was reported even for the low DE dose compared to warfarin. The risk of bleedings in the elderly is mitigated by dosing recommendations. As for the primary endpoint (stroke/SEE) the benefit of DE vs. warfarin also decreased by improved warfarin treatment and INR-control (TTR≥ 70%). This was particularly true for the elderly patients aged ≥ 75 years. The risk of MBE was markedly higher with DE compared to warfarin (yearly rate for DE110 bid

4.26%, for DE150 bid 5.14% and for warfarin 3.58%). The advantage of well controlled warfarin is also reflected in the NCB (composite of stroke, SEE, PE, acute MI, all cause death and MBE) in patients aged ≥ 75 years. However, a significant advantage of warfarin over DE is not evident in any of the provided subgroup analyses.

GI bleedings and GI AEs: GI bleedings occurred notably more frequent in patients randomised to DE. The yearly event rates of GI MBEs were dose dependent for DE (DE110 bid 1.11%, DE150 bid 1.57% vs. 1.07% for warfarin). The increased risk for DE150 bid vs. warfarin was statistically significant (HR=1.47 (95% CI: 1.17, 1.85; p=0.0008). A clear separation of the DE150 bid Kaplan-Meier curve in favour of warfarin was apparent after just a few days of treatment. The separation remained throughout the study. This significantly increased risk also included GI life-threatening MBEs and "any GI bleeds". For both DE dosages post-hoc sub-group analyses of GI MBE suggested that patients <75 years had lower risk of GI MBEs whereas patients aged ≥75 had a significantly higher risk with DE 150bid when compared to warfarin. The risk of GI bleeding is an issue of concern for patients ≥ 75 years but does not change the overall risk benefit of dabigatran. This safety issue necessitated a strong warning in the SmPC, section 4.4. Gastrointestinal adverse events dominated the adverse event profile of dabigatran in this indication, mainly represented by dyspepsia, nausea, abdominal pain and gastritis.

Myocardial infarctions: Another risk is the numerically increased risk of MI for patients randomised to dabigatran when compared to warfarin, although the risk was small in absolute terms (0.81%, 0.82% and 0.64% for DE110 bid, DE150 bid and warfarin, respectively). The increased risk of MI associated with DE (both dosages) vs. warfarin does not seem to decrease over time. No clear pattern was observed when analysed by baseline demographic characteristics, stroke risk factors, $CHADS_2$ score, AF type, baseline medication use or by medication use during study period. A dose response for the risk of MI could not be confirmed. In order to put MI into perspective of other outcomes, yearly event rates and absolute differences to warfarin for several patient sub-groups with high risk of MIs were provided (previous MI; history of CAD and age ≥65 years; diabetes and age ≥65 years; heart failure; LVEF <40%; moderate renal dysfunction). Based on these analyses the benefit of DE on the ultimate outcome of death, still compares favourably to the increased risk of MI. The pathophysiological mechanism is still unclear and markers that could reveal rebound anticoagulation have not been collected, but the generation of hypotheses is expected from a further sub-study of RELY which is pending (1Q-2Q of 2011). The numerically increased risk of MI with dabigatran is not considered to change the net benefit of DE vs. warfarin. Adequate warning was introduced in section 4.4 of the SmPC. Furthermore, MI is covered as a potential risk in the RMP.

Hepatic function: Patients with active liver disease (including patients with ALT or AST or Alk. Phosphatase elevations 2x upper limit of normal (ULN)) as well as patients with liver enzyme elevations on ximelagatran were excluded from the RE-LY study. In view of the potentially lifelong treatment the follow-up time in the RELY trial was considered limited. A more detailed analysis was performed by the MAH on the events of severe LFT elevations, Hy's law cases and hepatic AEs of interest (hepatic lesions, fatal hepatic failure and deaths with LFT elevations). The data confirm the low potential of hepatotoxicity of DE.

Patients with GI disorders requiring PPI: For patients "on PPI only during treatment" an increased risk for major GI bleed was observed (6.2%, 10.2% and 8.2% for DE 110bid, DE 150bid and warfarin, respectively). The risk seemed disproportionately higher for DE 150mg bid vs. warfarin for patients "on PPI only during treatment" compared to patients "never on PPI" and "on PPI at baseline". It is likely that caution should be given for patients on PPI upon initiation of DE treatment as well as for patients on DE who experience symptoms or signs necessitating initiation of PPI treatment. The lower dose of DE may be appropriate in these cases.

- Uncertainty in the knowledge about the unfavourable effects

Renal impairment: Patients with severe renal insufficiency have not been studied in RELY. This is already a contraindication for the use of Pradaxa. Patients with moderate renal failure were at increased risk of bleedings in both treatment groups with no evidence of dose-effect relationship, however, based on clinical data, no dose-reduction is considered necessary in the SPAF indication.

Pulmonary embolism: Apart from the increased risk for MIs, there was also a weak signal for an increased risk of PE with DE. PE is covered as a potential risk in the RMP.

Body weight: The rate of MBEs increased by decreasing body weight in all treatment groups however, there was no obvious impact of weight on the benefit risk of dabigatran vs. warfarin in this indication.

Biological monitoring test/antidote: An appropriate biological test that display a linear relationship with plasma concentrations, with a high level of sensitivity and that allows comparisons between laboratories is essential for drug monitoring. The Hemoclot assay is a diluted thrombin time coagulation assay which can be calibrated with lyophilised dabigatran standards for quantitative assessment of dabigatran concentrations in plasma. The Hemoclot assay is now available on the market.

Guidance has also been provided in the SmPC on how to handle DE before and after surgical interventions, in emergency situations and overdosing, and when switching from other anticoagulants to DE.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Systemic embolism and in particular strokes are important outcome parameters in prevention therapy in patients with non-valvular AF due to the most often disabling nature of these events. Estimated annual incidence of stroke in the non-treated AF population ranges from 2-5% per year in moderate risk subjects to 5-10% per year in high risk subjects. In view of these considerations the clearly favourable efficacy of DE vs. warfarin on strokes across all age groups including both ischaemic (constituted the majority of the strokes) and haemorrhagic strokes is considered clinically meaningful.

The limitation of effective anti-thrombotic therapy is the bleeding risk. Particularly the risk of major- and life-threatening bleedings is of importance, as this can lead to a higher risk of morbidity and death. The increased risk of MBE in the elderly population ≥ 75 years of age for DE vs. warfarin is considered of major clinical relevance due to the fragility of this population. In addition, the risk may potentially affect the sub-populations of patients at high risk of bleeding or with expected higher exposure to DE (e.g. moderate renal failure, female gender, low body weight).

The risk of GI MBE bleedings was significantly higher for DE (150 mg) vs. warfarin. In addition, an increased risk of MIs seems to be associated with DE treatment. These unfavourable findings must be counterbalanced against the beneficial effects.

It should be noted however, that life-threatening bleedings were significantly reduced for either dose of DE compared to warfarin. In addition, the data presented on all-cause mortality (analysed as a secondary efficacy endpoint) are reassuring. For patients allocated to treatment with DE110 bid or DE150 bid the relative risk compared to patients treated with warfarin was 0.91 ((0.80-1.03), p=0.1308) and 0.88 ((0.77-1.00), p=0.051), respectively. The data for vascular death were 0.90 ((0.77-1.06), p=0.2081) and 0.85 ((0.72-0.99), p=0.043), respectively.

- Benefit-risk balance

The overall risk of strokes has decreased in recent AF trials due to improved treatment of risk factors such as hypertension and heart failure. In view of this, the reduced risk of stroke/SEE in DE150 bid treated patients vs. warfarin treated patients is a significant clinical benefit. Also of clinical benefit is the decreased risk of intracranial haemorrhage, the perhaps most serious and devastating bleeding complication with VKA. Although absolute reductions were small, the relative reductions in comparison to warfarin were marked and consistent across a large variety of sub-groups.

Clinically important is also the fact that the favourable outcome on the primary efficacy outcome seemed not counterbalanced by an increased risk of major bleeding, at least in patients aged less than 75 years. The increased risk of bleeding in the elderly ≥ 75 years and in particular ≥ 80 years is worrisome due to the fragility of this population. Specific dosing recommendations are warranted for this population to mitigate this risk. Warnings for patients at high risk of bleeding as well as for patients expected to have higher exposure to DE (female gender, low body weight, moderate renal failure, concomitant use of P-gp inhibitors) have been included in the SmPC.

Dabigatran was associated with an increased risk of gastrointestinal bleedings (including all GI bleedings, GI MBEs and GI life-threatening bleedings). GI bleedings were associated with concomitant medication with ASA, clopidogrel, and NSAIDs, additionally to GI disorders requiring treatment with PPI and H2 blockers. Moreover, a significant interaction of major GI bleed for age ≥ 75 years was observed. The risk of GI bleedings did not change the overall benefit of DE vs. warfarin and specific dosing recommendations for the elderly as well as for certain sub-groups (subjects with known gastritis, esophagitis, or gastroesophageal reflux; subjects experiencing gastritis, esophagitis or gastroesophagial reflux while taking dabigatran; patients treated with proton pump inhibitors or H2 blockers) were implemented in the SmPC.

The pathophysiological mechanism behind the numerically increased risk of MI associated with DE treatment is not understood. Despite the potential serious outcome of such events, the overall benefit risk of DE is not considered affected by this finding due to the beneficial effect on stroke/SEE and in particular ICH. However, strong warnings have been inserted in the SmPC and MI has been included as a potential risk in the RMP.

In addition to the above discussion, the reduced risk for all cause death is reassuring though the difference vs. warfarin for either dose of DE was not statistically significant.

It should also be noted that global INR control in RELY, although being comparable to contemporary trials in this indication, was not optimal from a Northern/Western European standard. When MBE were analysed by time in therapeutic range (TTR) the outcome of warfarin treatment for the overall population improved with increasing TTR. For centres with TTR ≥ 70% the MBE rates were marginally higher for DE150 bid vs. warfarin. Still, for this population the rates of stroke/SEE, stroke/SEE/death and ICH were in favour of DE150 bid when compared to warfarin. Thus, due to the devastating effects of ICH the B/R of DE150 vs. warfarin is positive also when compared to well controlled warfarin treated subjects.

Also GI AEs were considerably more frequent with DE compared to warfarin. These adverse events may result in poorer compliance and risk of under-treatment. GI AEs occurred with approximately the same magnitude in the pivotal VTE prevention trials as in the RELY trial, however, in the VTE program they were not more frequent as for the comparator enoxaparin.

Discussion on the benefit-risk balance

Overall, both efficacy and safety of DE110 bid and warfarin in the prevention of stroke in nonvalvular atrial fibrillation was considered by the CHMP comparable. The superior efficacy of DE 150 bid vs. warfarin on primary endpoint (stroke/SEE) and on ICH was considered of major clinical relevance.

3.20. Prevenar 13

Benefits

Beneficial effects

The currently available 23vPS vaccine has shown efficacy against invasive pneumococcal disease in elderly. Therefore this vaccine serves as an acceptable control for this indication. The MAH has chosen to compare the immune responses to Prevenar 13 and 23vPS vaccine using OPA. OPA measures functional antibodies and is considered the best available option for serological comparisons between the two vaccines. In children and infants the OPA responses were shown to correlate to protection against IPD after vaccination with the 7-valent pneumococcal conjugate vaccine. Although the clinical picture differs somewhat between children and adults, it is very likely that protection is mediated through the same mechanism, i.e. opsonising antibodies. The ad hoc expert group also concluded that it is reasonable to accept OPA responses as a surrogate marker for vaccine efficacy in IPD.

It is acknowledged that no protective threshold for prevention of invasive disease has been defined in adults, but a non-inferiority comparison is considered valid.

The immune responses as measured with OPA to the 13vPnC vaccine have been shown to be non-inferior to the responses to the 23vPS vaccine for the 12 common serotypes, and for several of these serotypes the responses were also superior. The immune response to serotype 6A, which is unique to the 13vPnC vaccine, has been shown to be similar to the responses to the other 13vPnC vaccine serotypes. Consistent results were obtained in naïve subjects 60-64 years, and ≥65 years, as well as subjects ≥70 years of age who had received 23vPS vaccine more than 5 years previously. The immune responses to the 23vPnC vaccine in subjects 50-59 years of age were shown to be non-inferior to those in older subjects.

Thus, the demonstrated non-inferiority of the OPA responses of the 13vPnC vaccine to the 23vPS indicates that the 13vPnC vaccine also has at least the same immediate protective efficacy against invasive disease caused by the common serotypes.

A conjugate vaccine is expected to have benefits over a polysaccharide vaccine, in terms of boostability, immunological memory and generally improved immune responses, due to the T-cell dependent characteristics of the immune response. The 13vPnC vaccine has demonstrated all these characteristics in children, and fundamental differences in adults are not expected. The recently submitted data from study 6115A1-004 indicate that the 13vPnC vaccine induces immunological memory in subjects 60-64 years of age as well, while the 23vPS vaccine clearly does not. The duration of the immunological memory has been demonstrated 3-4 years after primary vaccination.

A negative effect of the 23vPS vaccine on subsequent vaccination with 13vPnC or 23vPS vaccine one year later has consistently been shown (hyporesponsiveness). Hyporesponsiveness was not seen following the administration of 13vPnC vaccine.

The study population included healthy subjects, and immunocompetent subjects with stable underlying conditions.

The immune responses to trivalent influenza vaccine administered concomitantly with the 13vPnC vaccine were very similar to the responses to influenza vaccine given alone. Likewise, the responses to the pneumococcal antigens were non-inferior with the exception of serotype 19F in study 3008, which indicates that the two vaccines may be given concomitantly.

Uncertainty in the knowledge about the beneficial effects

The protective efficacy against non-invasive disease (e.g. community acquired pneumonia) has not been clearly demonstrated for the 23vPS vaccine. The efficacy has been limited and inconsistently shown in several published clinical studies. The ad hoc expert group concluded that it will not be justifiable to claim efficacy of 13vPCV against other (non-invasive) pneumococcal infections based only on comparison of serological responses. Therefore, it is currently unknown if Prevenar 13 protects against CAP. However, a Phase 4 Clinical Trial (CAPiTA) of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease is currently ongoing, and the results are expected in December 2013.

The duration of immunity is currently not known. Data on antibody persistence is currently limited to one year, and preliminary data on immunological memory are limited to 3-4 years.

Data in high-risk immunocompromised populations is currently lacking. The clinical studies in elderly included healthy subjects and subjects who were immunocompetent with stable underlying conditions.

The relative value of improved immune responses of the 13vPnC over the broader strain coverage of the 23vPS vaccine is a very important issue. The data described previously from the USA and England and Wales demonstrates that the coverage of the 13vPnC vaccine decreased from around 70% to 50% when pneumococcal vaccination with 7vPnC was introduced in the childhood vaccination program. This is likely to be attributed to herd protection, i.e. decreased circulation of the vaccine strains. This also affects the coverage of the 23vPS vaccine, as 12 of the serotypes are common to both vaccines.

Epidemiological surveillance to ensure early detection of serotype replacement is considered of outmost importance. The MAH has committed to report the results of ongoing surveillance. Serotype replacement has been seen as a result of childhood vaccinations, and may occur regardless of adult vaccinations.

Risks

Unfavourable effects

There are no differences in the safety profile of 13vPnC in adults and older adults as compared to that observed in the young population. Furthermore, the safety profiles of 23vPS and 13vPnC are also similar and no new or significant safety issues have been identified when comparing the two vaccines in the present study populations.

The local reactions are generally slightly higher with 13vPnC as compared with 23vPS and more pronounced in the younger group i.e. 59-64 years. The incidence is higher in males. The gender difference is not so pronounced for systemic adverse events and not considered to be of clinical relevance.

Comparatively few serious adverse events were observed in the submitted studies. One case of GBS in the older populations was described as were one case of idiopathic thrombocytopenia, one case of lupus erythematosus and a few cases of arthralgia. This may indicate activation of autoimmune

disease. Adverse reactions such as rash, injection site reactions, pain, pyrexia, myalgia, arthralgia, headache and fatigue are all listed in the summary of product characteristics. One case of sleep apnoea was described at the 6 month follow-up visit (Apnoea in very premature infants (≤ 28 weeks gestation) is listed for 13vPnC.)

Uncertainty in the knowledge about the unfavourable effects

Further close monitoring of all cases of autoimmune reactions must continue. The predisposition for activation of such reactions is pronounced in the referred study population including older age groups.

The size of the safety database may be too small to detect rare AEs occurring at a frequency lower than 0.1%. For this reason, the MAH should provide safety data from the ongoing study (CAPiTA, 6115A1-3006) as a post-marketing commitment.

Balance

Importance of favourable and unfavourable effects

Invasive pneumococcal disease is an important health problem in the elderly population. The annual incidence of IPD in subjects ≥65 years is reported to be from 24 to 85 cases/100 000 population (WHO position paper: 23 valent pneumococcal polysaccharide vaccine, WER 83: 373-384, 2008). The existing 23vPS vaccine is recommended in several EU countries with varying coverage. Several clinical observational studies have documented the efficacy of the 23vPS vaccine against IPD caused by vaccine serotypes. The protection wanes over 5-10 years, and revaccination is generally not recommended with shorter intervals than 5 years due to hyporesponsiveness following vaccination.

In Europe and the United States*, S. pneumoniae* is estimated to cause approximately 30–50% of community-acquired pneumonias (CAPs) requiring hospitalization in adults.

The non-inferiority to the 23vPS vaccine is considered relevant and acceptable surrogate for protection against IPD. However, the lack of proven efficacy against non-invasive pneumococcal disease by the 23vPS vaccine makes an extrapolation of efficacy of this indication to the 13vPnC vaccine inappropriate until further data is available.

The issue of strain coverage is considered very important, and needs close epidemiological surveillance in order to continuously assess the absolute benefit of vaccinating with the 13vPnC vaccine.

The safety issues do not involve any immediate unfavourable effects or exert any negative influence on the balance between favourable and unfavourable effects.

Benefit-risk balance

The expected benefit in terms of protection against invasive pneumococcal disease clearly outweighs the risk of adverse reactions in adults 50 years and older for Prevenar 13. The benefit is expected to be smaller in subjects 50-59 years as the risk of disease is greater from 60 years of age onwards, but the balance is still positive.

For non-invasive pneumococcal disease the benefit is not considered demonstrated currently, and therefore it is not possible to conclude a positive benefit-risk balance for this indication.

The benefit of giving Prevenar13 concomitantly with the seasonal trivalent influenza vaccine also outweighs the risk of increased reactogenicity.

Discussion on the benefit-risk assessment

A conjugate vaccine is expected to elicit an immune response with all the characteristics of a T-cell dependent response, e.g. IgG response, affinity maturation of antibodies with repeated exposure, induction of immunological memory, and long lasting immunity. The responses to free polysaccharide vaccines on the other hand are generally expected to be mainly IgM, in the absence of previous immune memory, of shorter duration and no immunological memory. Therefore, a conjugate vaccine has many advantages, especially in long-term protection. The immune responses to the primary vaccination were shown to be non-inferior or superior to most serotypes in the 13vPnC vaccine compared to the 23vPS vaccine, as expected. In recently submitted preliminary data there is a strong indication of immunological memory 3-4 years following a primary vaccination with 13vPnC. In the same study the 23vPS vaccine was clearly shown not to induce immunological memory.

The 23vPS vaccine was shown to induce hyporesponsiveness to subsequent vaccination, regardless of whether 23vPS or 13vPnC vaccine is used. The 13vPnC vaccine did not elicit immune responses to a subsequent dose that were superior to the responses to the first dose, which can be expected. The responses were very similar after the second and first dose when given one years apart. Considering that this vaccine has demonstrated all characteristics of a T-cell dependent antigen in children, it is unlikely that any other effect would be seen in adults. Final data from study 6115A1-004 are requested as well as longer term follow-up.

It is very likely that protection against non-invasive disease requires higher antibody levels than what is required for invasive disease, as the antibodies must transudate to the site of infection in order to protect. Therefore it is not considered possible to conclude on efficacy against non-invasive disease based on serological bridging to the 23vPS vaccine.

The benefit-risk balance of Prevenar 13 for prevention of invasive disease caused by *S. pneumoniae* is therefore considered positive. However, it is beyond the scope of the CHMP to conclude on the relative role of Prevenar13 versus the 23-valent vaccine. Whether one or the other vaccine, or both vaccines, should be used in national programmes is the decision of national authorities.

3.21. Prezista

Benefit

The benefit of a simplified treatment regimen with once daily DRV/rtv that provides improved patient convenience with enhanced compliance in the proposed treatment-experienced population with 0 DRV RAMs would be of appreciable clinical relevance provided that this benefit is unambiguously proven throughout the sought indication at large (including patients with increased risk disease characteristics).

Uncertainties concerning the benefit

The claimed benefit is not unambiguously proven throughout the sought indication at large i.e. patients with increased risk disease characteristics such as high viral load > 100,000 copies/ml, CD4 counts at the lowest range <50 even <100 cells (x 106/L), 0 number of susceptible NRTIs in the OBR, and clade non-B. In response, the MAH restricted the claimed indication in line with the CHMP request.

The long-term efficacy of DRV/rtv q.d regimen is unknown in the sought target group i.e. ART experienced adult patients with 0 DRV RAMs. At the CHMP request, this point is reflected in the SmPC. Following discussions with the MAH, the CHMP agreed that the Week-48 data from trial TMC114-C229

sufficiently support the DRV/rtv 800/100 mg q.d. indication in the restricted treatment experienced population of the revised SmPC and that an additional trial in this population was not deemed necessary primarily due to the constrained feasibility and the duration of recruitment for such trial.

Risks

The simplified once lower dosage with DRV/rtv 800/100 mg q.d compared to the approved DRV/rtv 600/100 mg b.i.d regimen in ART-experienced patients may potentially increase the risk of virologic failure due to the development of resistance to DRV and other PIs. Furthermore, a higher single dose may induce a higher rate of gastro-intestinal intolerance.

Uncertainties concerning the Risks

There is no insurance that the simplified once daily lower dosage with DRV/rtv 800/100 mg q.d, compared to the approved DRV/rtv 600/100 mg b.i.d regimen, in ART-experienced patients will not increase the risk of virologic failure due to the development of resistance to DRV and other PIs. Hence, at the CHMP request, the indication in section 4.1 of the SmPC was restricted.

At the CHMP request, additional PK/PD data were provided by the MAH. These data seem to indicate that this risk is limited to a minority of the patients. However, the number of patients with suboptimal exposure was larger in the 800/100 mg q.d group than in the 600/100 mg bid group. Hence, a warning in this regard was added in sections 4.4 and 4.5 of the SmPC for Prezista.

The larger number of patients with suboptimal exposure to q.d regimen compared to the 600/100 mg b.i.d regimen, which might increase the risk of virologic failure due to the development of resistance to DRV and other PIs, remain worrisome. Hence, the RMP was updated accordingly.

Benefit-Risk Conclusion

Based on the review of the clinical efficacy and safety, the CHMP considers that the benefit-risk balance for the variation application EMEA/H/C/707/II/32 for Prezista (darunavir) is positive for a restricted indication for "the treatment of HIV-1 infection in ART-experienced adults with no DRV resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with DRV in such ART-experienced adults genotypic testing should guide the use of DRV.

3.22. Remicade

Benefits

Beneficial effects

The SONIC study was performed to evaluate the efficacy and safety of infliximab as monotherapy and in combination with azathioprine in comparison with azathioprine monotherapy in the treatment of moderate active Crohn's disease defined as CDAI score ≥220 and ≤450. The study population (SONIC) was patients with a median duration of Crohn's disease of 2.3 years, with no previous resections and that were naive to both immunomodulators and biologic agents and had failed the first line therapy.

Corticosteroid-free clinical remission (patient with a CDAI score of <150 points; who had not taken oral systemic corticosteroids or budesonide >6 mg/day for at least the previous 3 weeks) was induced by infliximab treatment in Crohn's patients with active moderate disease in 44% of patients receiving monotherapy and in 57% of patients on combination therapy (infliximab plus azathioprine). The

corresponding figure for patients receiving azathioprine monotherapy was 30%. The primary endpoint was evaluated at week 26 of treatment and secondary efficacy variables supported the results. This time point is considered relevant, since it can take up to 3 months before full effect of azathioprine is gained. Similar results have also been demonstrated in subpopulations with different baseline status of corticosteroid (including budesonide >6 mg/day) and 5-ASA treatment response.

All patients included were naive to treatment with biologic agents and immunomodulators. Approximately 30-40% had received previous corticosteroid treatment, while the majority had been on 5-ASA. It was raised that since 5-ASA is not an effective treatment for moderate to severe CD, the full study population does not reflect completely the population in the proposed indication. Nevertheless additional analyses for complete corticosteroid-free clinical remission showed that the treatment response in the patient subgroups that mirrors the intended patient population (i.e. the group of patients who entered the trial using a criterion other than 5-ASA failure which includes patients who were either dependent on corticosteroids at baseline or those who had failed corticosteroids) is of the same magnitude as in other subgroups and of clinical relevance. The data show that irrespective of inclusion criteria used the outcome (primary efficacy endpoint) is similar in the treatment groups.

In patients with a longer median duration (7.5 years) in the ACCENT I study, clinical remission was likewise induced by infliximab. The efficacy was evaluated with two co-primary endpoints, proportion of patients at clinical remission at week 30 and time to loss of response through week 54.

Patients in the ACCENT I study were classified as having moderate active disease according to the CDAI scores (between 220 and 400) despite current or prior treatments with corticosteroids, aminosalicylates and/or immunomodulators.

Thus, overall beneficial effects have been shown for Crohn's patients at different stages of the disease; and in the different subgroups defined by the inclusion criteria. Furthermore, data from the SONIC study indicate that in patients with objective signs of active disease i.e. increased CRP (predefined analysis) and with endoscopic signs of mucosal lesions at baseline (post-hoc analyses) achieve a greater benefit of the treatment compared to patients with normal CRP levels and no lesions at baseline.

Uncertainty in the knowledge about the beneficial effects

The potential long-term beneficial effects of using infliximab in earlier stages of Crohn's disease have not been evaluated. It is not known whether early introduction of the treatment may induce a more sustained long-term effect (e.g. reduced need for surgery) and if the treatment may affect the natural course of the disease i.e. in preventing the changes of phenotype of the disease from predominantly inflammatory to stricturing disease. Follow-up on disease outcome is undertaken in ongoing registry activities (TREAT, ENCORE). Nevertheless, the currently available efficacy data are sufficient to support a change of the indication to include also treatment of moderately active Crohn's disease.

Apart from the activity of the disease, the localisation and behaviour of the disease are also important factors in the management of patients with Crohn's disease. The general knowledge of how these factors interact with both the course of the disease and the response to therapy remains limited. Such knowledge is beyond what is required in order to obtain an approval in use in Crohn's disease.

Risks

Unfavourable effects

Known unfavourable effects of infliximab are the increased risk of infections, including serious, and a potential risk of lymphoproliferative disorders or malignancies. Risk for demyelination is among more uncommon additional types of events of concern. Furthermore, some patients will develop antibodies

to infliximab, which might limit the future use of the compound, and is associated with increased frequency of injection reactions. These events are described and addressed in the approved product information. They are also addressed in the approved RMP and closely monitored through routine pharmacovigilance activities as well as additional surveillance through registries and studies as necessary.

Uncertainty in the knowledge about the unfavourable effects

It cannot be evaluated yet if earlier treatment would imply any long-term disadvantages for patients with Crohn's disease. Nevertheless the long term safety of infliximab is continuously followed on an ongoing basis through routine pharmacovigilance activities as well as additional surveillance through registries and long term safety follow-up studies as detailed in the RMP.

The safety of infliximab in comparison with the safety of alternatives in the long term is of importance. The MAH reviewed and discussed about the safety profile for AZA/6-MP and infliximab. Based on results from clinical studies and registries, when comparisons are made of groups of patients receiving AZA/6-MP only, infliximab only, and a combination of the two, a general pattern of increasing incidence of AEs is successively observed. This pattern is considered to partly mirror the severity of the underlying disease in the different treatment groups. This is also confirmed by the increasing numbers of AEs in the system organ class 'Gastrointestinal disorders' in these treatment groups. To what extent it explains the differences in overall number of AEs observed is not possible to elucidate fully.

From the TREAT registry, with its features of an observational study in mind, it is reported that there was increased incidences of leucopenia, aplasia pure red cell, and transaminase increased for immunomodulator only group, while the incidences were generally comparable in subjects receiving infliximab and neither infliximab nor immunomodulators. Also the incidences of GI serious SAEs of obstruction and stenosis were generally higher in the immunomodulator only group, compared with infliximab groups, as well as hepatic events. In contrast, infections (including serious), and infusion reactions, as well as demyelinating events (a total of 3 patients in the 2010 report) were more often observed with infliximab.

With respect to malignancy/lymphoproliferative diseases, there are several reports in the literature concerning an increased risk for such conditions with the use of the thiopurine immunomodulators. This risk is also known with use of infliximab as detailed in the product information and monitored in the RMP. In the TREAT registry, there were no clear differences between the use of immunomodulators and infliximab (events per hundred patient years). It is interesting to note the publication summarising hepatosplenic T-cell lymphoma in IBD patients treated with infliximab and thiopurine analogues (Kotlyar et al., *Clin. Gastroenterol. Hepatol.* 2010). Among 36 cases analysed, all had received thiopurine analogues, either as monotherapy or combination therapy with anti-TNF agent, while none had received anti-TNF as monotherapy. Overall, there is no indication that infliximab carries a higher risk for malignancy/lymphoproliferative events than 6-MP /AZA.

The presented data show that treatments with both 6MP/AZA therapy and infliximab are connected with a number of potential serious adverse events and risks that are specific for each therapy. It is not possible to predict from the presented data on a group level which treatment is the safest for the individual. Nevertheless, it can be concluded that infliximab overall does not have a worse safety profile than AZA/6-MP.

Balance

Importance of favourable and unfavourable effects

Infliximab treatment has been shown to be effective in Crohn's disease patients with both moderately and severely active disease. Although the majority of included patients did not fully correspond to the

proposed indication, the presented revised analyses show a similar response also in the subgroup that mirrors the intended patient population. Corticosteroid-free remission has been demonstrated for up to one year in patients responding to the treatment. Thus, the treatment has a steroid-sparing effect. The SONIC study showed that infliximab, as monotherapy and in combination with AZA, had better efficacy results than AZA monotherapy. Although long-term benefits of treatment of moderate CD are not known, the potential effect of delaying stricturing and penetrating disease would imply an additional benefit for the patients.

The treatment is considered to be an alternative for patients who have previously been steroid-refractory, -dependent, or intolerant. For active colonic Crohn's disease for patients that have relapsed (corticosteroids) infliximab is also regarded as an appropriate option with or without immunomodulator for patients with objective evidence of moderate or severe disease.

The new data from SONIC did not reveal any new safety signals with infliximab. The experience from two registries is reassuring with respect to long-term safety. In these registries, there are no clear differences compared with patients treated with other conventional therapies, despite that patients on infliximab have more severe disease than comparators. The known potential risks (e.g. malignancy) and identified risks (e.g. serious infections, lymphoma, including the risk for hepatosplenic T-cell lymphoma) will continue to be closely followed through routine pharmacovigilance activities and additional surveillance through registries and studies as detailed in the RMP.

Benefit-risk balance

Clinically relevant efficacy, in both patients with earlier and later stages of Crohn's disease, has been demonstrated. The SONIC study shows improved effect compared with AZA as monotherapy. There were no new safety signals identified during the study period. There is also now relatively extensive experience from two registries (TREAT and ENCORE), which supports an acceptable safety profile. A comparison of the safety profiles of infliximab and 6-MP/AZA reveals that these two treatments have different main safety risks, and it can be concluded that infliximab does not have an overall worse safety profile than 6-MP/AZA.

To conclude, infliximab treatment has been shown to be effective in Crohn's disease patients with both moderately and severely active disease and presented data further support that the long-term safety of infliximab is not worse than other treatment options. The benefit-risk balance is therefore considered positive.

3.23. Revatio

The main study in the current application study A1481131 is the largest placebo-controlled paediatric study conducted so far, recruiting around 230 drug-naive patients and lasting 5 years.

The pivotal study A1481131 was a double-blind, multi-center, placebo-controlled parallel-group, dose-ranging paediatric study in PAH subjects, aged 1 to 17 years, body weight ≥8 kg, with different doses of sildenafil for 16 weeks. The primary objective was to assess peak VO2 in subjects who were able to perform the CPX test. However, all subjects who entered the study were assessed for haemodynamics, WHO functional class and the QoL measurements. A total of 234 subjects were treated with one of the 3 sildenafil doses (low, intermediate, high; according to body-weight ranges) or placebo and 115 children were able to perform CPX testing.

Interim efficacy and safety data from Study A1481156 the long-term extension study including subjects who completed Study A1481131 are also provided to support the above data.

The proposed dose based on the PK/PD simulations is accepted. The medium dose shows the best results in exercise testing accompanied with an acceptable safety profile.

The choice of endpoints in adult PAH is a recognized problem, and is even more complex in the paediatric population, due to the scarcity of patients and their inability to perform exercise testing.

Haemodynamic parameters are considered by some experts to be the appropriate primary endpoints for paediatric studies, considering the difficulty in performing exercise tests**.**

The main outcome Peak VO2 after cardiopulmonary exercise (CPX) testing has shown to be useful to assess patient prognosis and as a mean to quantify functional capacity, although experience is limited at present. Therefore, the peak VO2 should be interpreted in association with other harder endpoints (i.e., mortality, time to clinical worsening) and invasive haemodynamic measurements, leading to additional post hoc analysis requested to the applicant during the procedure.

It is concluded that efficacy data based on improvement of exercise capacity or pulmonary haemodynamics support an indication for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

The currently proposed indication reflects the results of the paediatric study and is generally formulated in line with the adult indication, except for omitting the WHO classification. The CHMP opted for this omission as the representation of the paediatric study (more WHO I and less WHO III) is different from that shown in adult studies. Furthermore, the ESC treatment guideline for PAH does not recommend specialized intervention in WHO I, however, this is mainly based on adult data. In the A1481131 study, improvement in haemodynamic parameters was shown in all three functional classes, but results on VO2 max were inconsistent. There are experts who advocate early intervention in paediatrics (earlier than WHO II) considering that deterioration in paediatric patients is more rapid. However the number of patients with WHO 1 in the pivotal A1481131 study is too limited for any definite conclusions on the Benefit/Risk in this specific subgroup.

No new safety issues were identified with long term use of sildenafil in paediatric PAH patients.

It is important to highlight that the approval of this suspension for extemporaneous formulation is an interim measure temporally accepted. The MAH has committed to develop a suitable age appropriate formulation in a form of a powder for oral suspension (POS) which is currently under development.

In conclusion, based on the data provided in this application, the CHMP considers that the benefit/risk of Revatio is positive in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

3.24. RoActemra

Benefits

Beneficial effects

The following beneficial effects were investigated in the clinical studies with tocilizumab:

Treatment of symptom and signs: Endpoint for evaluating this benefit is the response for JIA ACR30 and absence of fever. This response was met in 85.3% (95% CI 77.3 – 93.3%) of the total tocilizumab

treated population compared to 24.3% (95% CI 10.5 – 38.1%) in the placebo population. More stringent criteria (JIA ACR50, JIA ACR70, JIA ACR90) confirm this effect.

Correction of anaemia: Anaemia is caused by a combination of factors in long standing disease. It could therefore be regarded as a surrogate of disease activity although it has not been validated for this use. Of those placebo treated patients that had anaemia at baseline 2/29 (6.9%, 95% CI 0.0 – 16.1%) had normal haemoglobin at week 12. In the total tocilizumab treated population 40/50 (80%, 95% CI 68.9 – 91.1) had normal haemoglobin at week 12.

Decrease of concomitant corticosteroid therapy: The protocol allowed reduction of corticosteroid dose if JIA ACR70 response was met at weeks 6 or 8. One/31 (3.2%, 95% CI 0.0 – 9.4%) placebo patient and 17/70 (24.3%, 95% CI 14.2 – 34.3) tocilizumab treated patients reduced their oral corticosteroid dose by 20% to week 12 without experiencing a flare.

Remission of disease symptoms: The most stringent criterion is a JIA ACR90 response, this was met by 2/37 (95%CI 0.0 – 12.7%) in the placebo group and 28/75 (95% CI 26.4 – 48.3%) in the total tocilizumab group.

Functional improvement: For the assessment of functional improvement in daily live CHAQ-DI was used. 58/75 (77.3%, 95% CI 67.9 – 86.8%) TCZ patients and 7/37 (18.9%; 95%CI 6.3 – 31.5%) placebo patients had a minimally important improvement (0.13) in CHAQ-DI score from Baseline to Week 12.

Uncertainty in the knowledge about the beneficial effects

With regard to these investigated beneficial effects, the following observations were made:

Treatment of symptom and signs: Sources of uncertainty are related to the population recruited and the rather pronounced effect on CRP and fever with the potential of unblinding. However, given the results of the conducted sensitivity analyses and the magnitude of the treatment effect there is little uncertainty for these beneficial effects. Even a halving of the effect size would be regarded as clinical meaningful in this patient population if statistical significance were demonstrated. It is interesting to note that the physician component and the parent component appear to be diverging in the sense that in the placebo group physician evaluation is stating improvement over time whereas the parent evaluation appears to indicate no large change in disease severity.

Correction of anaemia: Correction of anaemia is not an accepted surrogate for disease activity in sJIA. However for a condition with chronic inflammation and ensuing anaemia this endpoint constitutes a valuable confirmation of the beneficial effect. Since this is a rather objective endpoint uncertainties mainly relate to the possibility of transfusion in extreme cases. It is difficult to define clinically meaningful changes. LLN is an obvious choice for a cut-off.

Decrease of concomitant corticosteroid therapy: In a blinded trial this is considered clinically as a very relevant endpoint. Of note, any changes from baseline could result in increased disease activity and would therefore impact on the primary efficacy endpoint. Source of variability are mainly compliance with the treatment regimen.

Remission of disease symptoms: Similarly to the above "symptoms and signs" evaluation main sources of uncertainty is the population recruited into the trial and the potential for unblinding. From the supportive data the remarkable increase over a longer time period increases the confidence in the 12 week data.

Functional improvement: Uncertainties mainly relate to the term "minimally important improvement". Robustness of the effect could be questioned. The effect size and the conditions under which it was obtained are not considered to be a relevant source of variation.

In addition, there are some potential beneficial effects of tocilizumab in systemic juvenile idiopathic arthritis, which would however require additional data either long-term of with larger sample sizes:

Prevention of MAS, decrease in mortality: This would be a clear-cut endpoint requiring a large sample size. From the obtained data no judgement can be made. Further data, e.g. from registries will be collected to obtain a larger sample size. Uncertainties relate to the difficulties in diagnosis, the multiple triggering mechanisms and the multi-modal treatment. Furthermore, an investigation of the primary or secondary influence of tocilizumab in the risk for developing MAS will be addressed in the post-marketing observation period, within the context of the ongoing Part II and Part III of study WA18221 as detailed in the RMP.

Prevention of structural damage: This would be the most important beneficial effect as regards the arthritis component of the disease. No long term data are available therefore it is uncertain whether this beneficial effect can be obtained. Data from adult rheumatoid arthritis make it more likely that also a beneficial effect can be demonstrated.

Preservation of bone integrity: sJIA is associated with osteoporosis but the role of IL-6 in bone metabolism is not well defined and the current data are conflicting. In order to dissect the potential detrimental effects of IL-6R inhibition on the bone long term data are needed evaluating e.g. the effect of therapy on bone mineral density. Data on concomitant corticosteroid use are needed. The MAH is going to address this with the long term data of WA18221 (phase II and III) as detailed in the RMP.

Resumption of growth and physical development: This highly relevant beneficial effect requires long term data that are not available but will be collected in the long term extension of WA18221 as detailed in the RMP.

Remission of disease: Based on the available data it is uncertain whether inhibition of IL-6R is necessary long-term or whether remission can be obtained without treatment with tocilizumab after a defined treatment phase. The MAH is planning to address this in part with the investigation of different dosing regimen in the extension phase (Part III of study WA18221 will assess the long-term durability and magnitude of the tocilizumab efficacy response in patients with sJIA including meeting the definition of inactive disease and clinical remission) as mentioned in the RMP.

Decreased inflammatory burden, Prevention of amyloidosis: Amyloidosis is a rare complication nowadays. From the demonstrated effect of tocilizmab treatment on SAA there is little doubt that amyloidosis could be prevented if it were still a major clinical problem. More difficult is the question whether a "decreased inflammatory burden" will decrease the cardiovascular risk in the future.

Risks

Unfavourable effects

Overall, the qualitative safety profile of tocilizumab in children as demonstrated in the data for systemic idiopathic arthritis appears to be generally comparable to data on rheumatoid arthritis in adults. The following unfavourable effects were observed:

Infection: Infections are in general increased in tocilizumab treated patients. Serious infections occurred with increasing incidence in the longer term studies. For the long term extension of the pivotal trial SAE infections and infestations are reported with 11.3 per 100 patient years. The main

confounding factor is concomitant corticosteroid use. Based on the type and severity of infection observed thus far, with the exception of bacterial arthritis and pneumonia, there is no specific concern. Bacterial arthritis has been reported to be more common in adult patients with rheumatoid arthritis, whether this is the case in children is unknown. The SmPC provides adequate guidance under "Special warnings and precautions for use"; also the educational programme addresses this safety aspect.

Anaphylaxis: Life threatening anaphylaxis has occurred in one patient in the placebo controlled part. This is a medically highly significant event. The SmPC as well as the educational programme provide adequate guidance on serious hypersensitivity reactions and their management.

Neutropenia: Neutropenia is clearly increased in tocilizumab treated patients, it is reversible on discontinuation and not unfavourable per se, it is the assumed association with infection that defines its role as unfavourable. Relevant information is provided in the SmPC and the educational programme.

AST/ALT/bilirubin elevation: In general, the medical significance of the observed elevation of transaminases and bilirubin is unclear. Guidance for monitoring of these laboratory changes is provided in the SmPC.

Thrombocytopenia: Thrombocytopenia has been observed, which could be a medically important event if associated with bleeding. The SmPC indicated these aspects.

Hypercholesterolaemia: Hypercholesterolaemia is a cardiovascular risk factor. Small increments are noted for the total population, for individuals with a high baseline this increase could become relevant. Guidance for monitoring is provided in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

As established for tociliziumab for the adult indication, there are areas with uncertainty about the unfavourable effects. These are addressed in the SmPC and through risk minimisation activities described in the risk management plan, as appropriate. Regarding the above indicated unfavourable effects observed in the paediatric studies to support the present extension application, the following observations are made:

Infection: The uncertainties relate to the unknown potential for serious opportunistic infections and the unknown incidence of fatal infections. This issue is closely related to MAS (see below) and to neutropenia.

Anaphylaxis: It is an unfavourable effect that cannot be predicted based on pre-clinical data. So far immunogenicity appears not to be a common occurrence but this may change with different background therapy e.g. reduced corticosteroid use. Uncertainties relate to the difficulty in diagnosing hypersensitivity reactions, they may in fact be underdiagnosed, and defining the most appropriate strategy for identifying patients that should be discontinued from treatment.

Neutropenia: Neutropenia is by general medical knowledge expected to be associated with infection. However, this relationship has not been unequivocally been established for tocilizumab. At present it is regarded that there is a high likelihood of a causal relationship between severe neutropenia and infection, however there is no proof from the data.

AST/ALT/bilirubin elevation: Uncertainties relate to the unknown consequences of long-time mild to moderate transaminase elevations. It is unknown whether a mere shift in baseline, that appears likely from the provided data, may have long-term consequences.

Thrombocytopenia: The occurrence is relatively well described however, the risk of haemorrhage is uncertain, but not regarded as high considering the data in paediatric population so far.

Hypercholesterolaemia: The increase in cardiovascular risk that would be attributable to long term cholesterol increase is unknown.

Further to these areas of uncertainties, there are other potential unfavourable effects:

MAS/HLH: MAS can be the consequence of insufficient treatment, but can also be triggered by infection and potentially by certain drugs. The occurrence of MAS in the main trial supporting the sJIA indication and the extension studies appears to compare favourably to literature data. However, the reported incidences cover a wide range and a clear picture could only be generated by a long term comparative trial which is not feasible. Triggering of MAS could also follow hypersensitivity reactions and infections, AE that could become more frequent with longer standing IL-6 receptor blockade. This safety aspect has therefore been added to the SmPC and to the educational programme.

Pneumothorax: From the mechanism of action the causal relationship of pneumothorax to therapy is uncertain. One possible pneumothorax with fatal outcome was observed. Considering the incidence of pneumothorax in general it is less likely that this is a chance event, although this cannot be excluded.

Hypogammaglobulinaemia: This was reported as an AE in a Japanese study, there are also cases flagged in the WA18221 study report. Hypogammaglobulinaemia is associated with an increased risk of infections. Uncertainty exists about the rate of occurrence long term because of lack of long term study data. If confirmed this conveys with a higher likelihood and increased risk of infections. This will be followed through routine pharmacovigilance activities and additional surveillance through registries and studies as detailed in the RMP.

Masking of infectious complications/ "false negative CRP": Efficient IL-6R blockade theoretically inhibits the acute phase response to infection, CRP for example could be a less reliable marker and fever response would also be attenuated. There is uncertainty whether these observed effects lead to a delay in the diagnosis of infections. In the end severity of infection would be a "composite" of the infection per se and the delay of diagnosis. The SmPC as well as the educational programme provide respective guidance.

Vaccine inefficacy: Interventions in components of the immune system harbour the risk of a decrease of wanted immunogenicity. In the absence of specific data with tocilizumab a dedicated study of the effects of TCZ on vaccination to evaluate the effects of tocilizumab on vaccination in subjects with active rheumatoid arthritis receiving background methotrexate is currently planned as detailed in the RMP.

Balance

Importance of favourable and unfavourable effects

There is a high unmet medical need for the treatment of patients with sJIA. The observed responses as regards symptoms and signs are very important and constitute the primary goal of any treatment. The strength of the data lies in an effect that could be regarded as remission in a considerable fraction of patients. Reduction in corticosteroid dose is another very important goal of treatment for the prevention of corticosteroid induced side effects. Correction of anaemia is of lesser importance but may be indicative of an influence on disease activity overall. Functional improvement by itself is of lesser importance.

The most important unfavourable effects are infections and neutropenia because of the risk of permanent consequences (e.g. joint destruction). As part of the pharmacovigilance activities, anaphylaxis needs to be monitored if the incidence of severe/serious reactions increases. Transaminase elevations are of importance because of the involvement of a vital organ and the unknown long term consequences. Thrombocytopenia without bleeding is of lesser importance and hypercholesterolaemia is considered less important for short term considerations, but needs to be monitored for long term benefit/risk considerations. The SmPC and the Risk Management Plan adequately addresses these safety-related topics. In addition, a dedicated educational programme provides information and guidance. In addition, the MAH will perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

Benefit-risk balance

The demonstrated beneficial effects on symptoms and sign of disease and associated functional improvement as well as the possibility to reduce corticosteroid treatment as demonstrated in the pivotal trial outweigh the most important risk of increase in infections, risk of neutropenia and transaminase elevation.

Discussion on the benefit-risk assessment

The benefit risk assessment is based on the short term data in a controlled setting and longer term uncontrolled data with a small sample up to one year. These data are considered appropriate based on a high unmet medical need in a disease with limited treatment options.

Overall, the efficacy as demonstrated with these data is considered of high clinical relevance. Because of the small sample size and the short follow-up there are uncertainties around the incidence of severe events such as anaphylaxis, serious infections, opportunistic infections and long term effect on the liver as well as the beneficial effect on disease activity. Nevertheless, these uncertainties do not offset the demonstrated beneficial effects and the potential beneficial effects on disease activity and long term outcome that may even be the true, although not obtainable, indicators of benefit for the patient. It is noted that the appropriate dose in the long term setting needs further monitoring; the applicant will investigate different dosing strategies in the ongoing extension of the pivotal trial as detailed in the RMP, which is deemed acceptable. The MAH will also perform a study to investigate the possibility of dose reduction for AE (thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients as detailed in the RMP.

It is necessary to generate long term data through a systematic collection of as many patient data as possible in a comprehensive fashion e.g. under registry conditions. Given that sJIA may be a life long disease in a subset of patient and given that a number of off label treatments are used in clinical practice it is important to follow these patients long term, in particular because disease complications that are usually reserved to the adult domain may become important, e.g. accelerated cardiovascular disease. The applicant will provide updates from several European registries including BSRBER, ARTIS and RABBIT.

The following indication is therefore agreed for section 4.1 of the SmPC:

"RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX".

3.25. Simponi

The MAH applies to add wording to the PsA indication, to reflect data on structural joint damage measured by X-ray. Changes to section 5.1 are also proposed. These claims are based on newly submitted X-ray data from the long-term extension of study C0524T08. This study was the basis for the initial approval of PsA.

The effect of golimumab on progression of joint damage was assessed using the Modified van der Heijde-Sharpe, which is considered to be a valid instrument for assessment of X-ray data, and has been used in other applications for the same claim. The primary X-ray analysis was undertaken by comparing 24 weeks placebo and golimumab results. Thereafter, all placebo subjects were switched to active treatment. There was also an option for early escape after 16 weeks. The study was well conducted with only 17% of patient discontinuing during 104 weeks and with no major difference in withdrawal pattern with respect to amount or cause.

Although the progression rate was limited in the placebo group due to the short duration (24 weeks), statistically significant differences in favour of active treatment was seen for mean change in Modified van der Heijde-Sharp score as well as for percentage of patients with no progression between baseline and week 24 (78.8% vs 62.7% for golimumab and placebo respectively). Considering the low withdrawal rate with no differential withdrawal pattern and consistent results in sensitivity analyses, there is no reason to question the robustness of these results.

Concerning maintenance of effect an increasing positive effect on structural damage cannot be expected in study C0524T08 since all patients were given active treatment from week 24. At best a sustained difference between patients initially randomised to active treatment and placebo could be expected, and the percentage of patients with no progression between baseline and week 52 and week 104 was similar to the responder rate at week 24 for patients initially randomised to active treatment.

Although the data is too limited to fully evaluate the clinical long term relevance of the golimumab effects on structural damage in patients with psoriatic arthritis it can be concluded that a substantial number of patients could experience beneficial effects on joint damage progression. It is further considered that essential support can be gained from RA, where more knowledge about joint damage progression is available.

Symmetric PsA shows greatest resemblance with RA, and in subgroup analyses performed by the MAH significant effects was observed in this PsA subtype only. This is consistent with experience from other anti-TNF agents for which an effect in subjects with symmetrical disease has been shown, while relevant effects in subjects with asymmetrical disease have been less convincing. Thus the claim on positive effects on structural damage has been restricted to the polyarticular symmetrical subtypes of PsA.

The MAH also applies for changes to section 5.1 of the SPC to include number of endpoints. The inclusion of PASI75 data was not agreed by the CHMP.

With respect to safety, the MAH has submitted long-term extension data from the open label study T08, which included data up to 2 years of treatment of PsA patients with golimumab. The already established safety profile of golimumab is confirmed. Infections, including some serious and severe, occurred in association with golimumab treatment. There were in total 8 malignancies reported; all in golimumab treated subjects. The large difference in duration of follow up between placebo (19.6 weeks) and golimumab (75-76 weeks) groups should be considered. Thus, these data are difficult to interpret, but a relation to treatment cannot be excluded. The product information and RMP address risk for malignancy, as well as the other well-established safety concerns related to treatment with an

anti-TNF agent adequately. Thus, the safety profile of golimumab is comparable with that already well established for anti-TNF agents. No new signals are identified.

The benefit-risk balance for Simponi is positive in this new indication. Furthermore, the submitted data do not modify the current benefit-risk balance.

3.26. Soliris

Benefits

Beneficial effects

Treatment with Eculizumab in the PT-resistant population (Study C08-002A/B) improved or stabilised the kidney function, haematological parameters and systemic manifestation as measured by QoL. The results were robust and compelling in these patients without therapeutic alternatives, since these patients were considered resistant to the usual treatment in aHUS (Plasma therapy). Overall, platelet counts increased and were within normal limits in 14 of 17 patients (82%; 95% CI: 57%-96%) during the eculizumab treatment period. The time to first occurrence of normal platelet count (150 x 109/L) occurred as early as one day following the first eculizumab dose, with a median time of 7 days to achieve a first occurrence of platelet count normalization. Regarding Haematologic Normalization, it was achieved by 76% of patients (95% CI:50-93%) and in up to 90% of the 10 patients with both abnormal platelet count and LDH at entry. Importantly, the duration of response continues into the extension phase, with a median duration of response limited only by the current data cut-off and is currently 258 days (range 196-431) for hematologic normalization and 267 days (range 217-389) for complete TMA response. Additionally, at the time of the data cut-off, 13 of the 17 patients in study C08-002A/B remained on treatment.

Results from the Study C08-003A/B, showed that a substantial majority of PT-sensitive patients receiving eculizumab in the study (16 of 20 patients [80%; 95% CI: 56- 94]) achieved the primary endpoint of TMA Event-Free Status through Week 26, which was sustained for a median time duration of approximately 40 weeks (280 days) as of the data cut-off date. Regarding Hematologic Normalization, it was achieved in almost all patients, demonstrating maintenance of normal platelet count after discontinuation of PT and start of eculizumab therapy. A total of 18 out of 20 patients (90%; 95% CI: 68-99) achieved Hematologic Normalization. 100% of study C08-003A/B patients who obtained hematologic normalization (and its components of platelet count normalization and LDH normalization) and complete TMA response indicating, that all patients who achieve an improvement in TMA, maintain that improvement with ongoing treatment. At the time of data cut-off, 19 of the 20 patients in study C08-003A/B also remain on eculizumab treatment.

Although no conclusion can be drawn on any potential benefit in renal function in the long-term, which is the ultimate goal of treatment, the available evidence support the use of eculizumab as an alternative to plasma therapy in the treatment of PT-sensitive population.

Efficacy in the paediatric population has been demonstrated throughout the evidence provided by the retrospective study C09-001 which included 30 patients. There were 15 paediatric patients and 4 adolescents. The efficacy of eculizumab as determined by measures of platelet count, TMA event free status, TMA intervention rate, haemoglobin and renal improvement was observed in all paediatric age groups from 2 months to 11 years. Almost all paediatric patients achieved or maintained a normal platelet count, including 6 of 7 patients who were thrombocytopenic (platelet count <150 × 109/L) before starting eculizumab. Similarly, 11/15 (73%) of paediatric patients achieved TMA event-free

status with eculizumab treatment. TMA intervention rate significantly decreased from a median of 0.45 events per patient/day in the 28 days prior to eculizumab to 0 on eculizumab (P<0.0001). None of these patients required new dialysis. Clinically significant improvement in renal function was also noted in eight (53%) pediatric patients, and a clinically significant increase in hemoglobin (>20 g/L) was also observed in 53% of pediatric patients.

Regarding the update from the prospective studies C08-002A/B and C08-003A/B (until 64-63 weeks), it is worth highlighting that the efficacy of Soliris was maintained, or even improved, in the long term.

Risks

Unfavourable effects

Nearly all patients experienced a treatment emergent adverse event. Generally speaking, the safety profile in both PNH and aHUS indications is similar. The most frequently reported AEs in the aHUS indication were: diarrhea (32% of patients), vomiting (22%), nausea (19%) and abdominal pain (11%), headache (30%), anemia (24%), Leukopenia (16%), hypertension (24%), infections and infestations (nasopharyngitis, upper respiratory tract and urinary tract infections), insomnia (14%) general disorders, administration site conditions, musculoskeletal and nervous system disorders (41%), vascular disorders (41%) and respiratory, thoracic and mediastinal disorders (30% of patients). There have been some AEs frequently described in aHUS indication (hypertension, insomnia and vascular disorders) that were not described with the same frequency in the PNH patients. However, in the CHMP's view the lack of control group precludes to determinate the actual frequency of these AEs and if they were related to the administration of Soliris or if the disease and concomitant therapy received might have contributed.

Serious AEs were reported in 20 (54%) patients treated in studies C08-002A/B and C08-003A/B. The most expected SAEs are those related to the immune systems. The four drug-related SAEs consisted of accelerated hypertension, hypertension and peritonitis.

The overall prevalence of infection in paediatric patients was 67% (N =10/15 patients) which was also similar to that observed in the adult patient group studied in the prospective studies (65%, N=24/37 patients). The following adverse events were noted to be more prevalent in the paediatric than in the adult population: tachycardia, eye disorders, diarrhoea and pyrexia.

The discontinuation of the treatment appears to induce a worsening of the disease, in many cases from an improved situation. This is considered as safety concern.

The frequency of the most commonly reported AEs appears to increase in the long term, particularly in the PT-sensitive population, although it is noted that the majority of AEs described in the updated report are non serious, and of easy management in the clinical practice. The relationship with eculizumab is difficult to be established, as no direct comparison exists. Some of the AEs are probably influenced by other baseline medicinal products, i.e. infections and infestations by immunosuppressant. On the contrary, other AEs could be attributed to the experimental drug. In this regard, it should be noted that AEs like diarrhoea, nausea, vomiting, fatigue, headache, hypertension, and infections might increase over time.

Balance

Importance of favourable and unfavourable effects

Treatment with Eculizumab in the PT-resistant population improved or stabilised the kidney function, haematologic parameters and systemic manifestation as measured by QoL. The results were robust and compelling in patients without therapeutic alternatives, since these patients were considered resistant to the usual treatment in aHUS (Plasma therapy). The clinical relevance of these outcomes has been convincingly demonstrated. The benefits clearly outweigh the known and potential risks of eculizumab that in general is well tolerated and the AEs profile of easy management in clinical practice.

In the PT-sensitive population eculizumab has demonstrated to be an effective alternative to plasma therapy. The benefit/risk balance is considered positive.

The evidence provided to support the indication in the paediatric population is limited and mainly based on retrospective data so far. However, the available results are consistent to those seen in the adult population, it is considered that these data are sufficient to establish a positive benefit-risk in the paediatric population. The limited database makes necessary a continuous follow-up and reassessment of the benefit/risk balance and therefore the PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Benefit-risk balance and Discussion on the benefit-risk assessment

The benefits showed by eculizumab in the treatment of aHUS (adults and children) outweigh the risk associated to this new therapy. The relatively high dose proposed in this indication raises some concerns and it is recommended to the MAH to further investigate the efficacy and safety of lower doses as post approval.

3.27. Synflorix

Benefits

Beneficial effects

Two doses of Synflorix were shown to elicit immune responses in children aged 3-4 years old in study 046, which are at least of the same magnitude as the responses to the approved 3+1 and 2+1 primary vaccination schedule in infants.

Uncertainty in the knowledge about the beneficial effects

There are limited data in children 48-60 months of age, and there are no data on children in this age group receiving two doses. The immune responses after two doses in children 3-4 years of age were lower than those seen in children of the same age who had received a priming course of 3+1 or 2+1 doses and a booster dose at 36-46 months of age. The implication of this lower response on long-term immunity is currently unknown. The lack of immunogenicity data following 2 doses in children >4 and <6 years of age are of some concern, but it is likely that immune responses in 2-4 year old children are also representative of children 4-5 years of age.

Risks

Unfavourable effects

The reactogenicity is generally similar to what has been shown previously in younger children. However, the frequency of pain at the injection site was shown to increase with increasing age in study 013.

Uncertainty in the knowledge about the unfavourable effects

There are no data on children 48-60 years of age receiving two doses. Considering the observed increased frequency of pain at the injection site in study 013, there is a need for more data on the risks. The MAH provided additional analysis from study 013 for age groups 24-35 months, 36-47 months, 48-59 months and 60-71 months, which do not indicate a clear increase in reactogenicity with increasing age, although the age segments are small, e.g. the 60-71 month group only includes 9 individuals. In addition, a Kenyan study in children 12-59 months of age do not support increased reactogenicity with increasing age. However, data in the oldest children, i.e. 48-60 months of age receiving two doses are scarce, and the MAH is requested to closely monitor adverse reactions in children 2-5 years and report in upcoming PSURs.

Balance

Importance of favourable and unfavourable effects

The incidence of pneumococcal infection is greatest among children below 5 years of age, and therefore there is a need to vaccinate this age group. The lack of immunogenicity data following 2 doses in children older than 4 years of age is a deficiency, but it is likely that the results from the younger children can be extrapolated to the older children. The lack of safety data in the initial dossier was identified by CHMP as a major objection, mainly due to the observed increase in frequency of injection site pain with increasing age. However, in response to the major objection raised, the MAH has presented additional data that do not support an overall increase in reactogenicity by increasing age.

Benefit-risk balance

The incidence of disease caused by *S. pneumoniae* is highest in children up to 5 years of age, thus there is a need to vaccinate children up to 5 years of age. The results of study 013 indicated that a single dose given to children over 2 years of age did not result in sufficient immune responses. In study 046, it was shown that 2 doses given to children 3-4 years of age resulted in immune responses that were at least comparable to the responses seen in younger children following primary immunisation. It is considered that the immunogenicity data from the 3-4 year old children can be extrapolated to children up to 5 years of age.

There was an increase in the incidence of pain at the injection site with increasing age in study 013, but no increase in systemic reactions. These data were not supported by a Kenyan study 070, which did not support increased reactogenicity with increasing age and by further analysis of the 013 data by age group. Thus, there is no specific safety concern with increasing age, and the safety data from younger children can be extrapolated to children up to 5 years of age.

Thus, the benefit of vaccinating children up to 5 years of age is considered to outweigh the risks of vaccination.

As the overall safety database in children 2-5 years of age is very limited, the CHMP recommended performing an active safety surveillance, and closely monitoring vaccine safety in this age group. All serious listed and unlisted adverse events should be continuously reported and accordingly be presented cumulatively in future PSURs.

Outcome

Based on the CHMP review of data on safety and efficacy, the CHMP considers that the benefit risk balance of Synflorix for active immunization against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants in children 2-5 years is considered acceptable.

3.28. Tarceva

Benefits

The EURTAC study is the first prospectively conducted, relatively large randomized, unblinded phase III trial comparing the efficacy of erlotinib to a standard platinum-based doublet regimen in the 1st line treatment of patients with EGFR activating mutations in Europe.

Following review of the interim analysis results of the EURTAC study, the IDMC recommended stopping of the trial after demonstration of a substantial benefit of erlotinib over chemotherapy. At the time the HR for PFS was 0.42 (95% CI 0.27-0.64, p<0.0001) which corresponds to a 58 % reduction in the risk of progression or death. The Kaplan- Meier curves make a clear and early separation. The median PFS for patients in the chemotherapy arm was 5.2 months vs. 9.7 months in the erlotinib arm resulting in an absolute gain of 4.5 months in median PFS in erlotinib-treated patients. This is considered a highly clinically relevant gain in PFS. The robustness of the result was confirmed in a number of sensitivity analyses, sufficient reassurance has been provided regarding the independent review process and consistent results were found in subgroups with an acceptable sample size.

Results from supportive trials and published literature confirm the findings of the EURTAC study.

Uncertainty in the knowledge about the beneficial effects

N/A.

Unfavourable effects

In conclusion, the overall safety profile of erlotinib given as 1st line therapy in NSCLC patients with EGFR mutated tumours is considered consistent with the known safety profile of erlotinib described in later lines of therapy where only a minority of patients happened to harbour EGFR mutations. The most commonly reported AEs in the 1st line setting in patients with activating mutations were rash and diarrhoea and the safety profile was overall manageable, although serious or severe events did occur, demanding dose reductions or interruptions. The discontinuation rate was low. No new safety signals have been identified.

Benefit-risk balance

The benefit of erlotinib in terms of PFS compared to standard chemotherapy regimens as first line therapy of patients with activating EGFR mutations is considered to be clinically relevant and well documented.

The safety profile of erlotinib is considered acceptable, well-characterized and distinct from the well-known safety profile of standard chemotherapies. The oral administration of erlotinib provides convenience to the patient.

3.29. Vectibix

Benefits

- Beneficial effects

In both phase III studies a statistically significant but modest increase in progression-free survival was observed in patients with wild-type KRAS tumours. There was a small absolute difference in median survival (1.4 - 1.8 months) and hazard ratios around 0.80 in the most mature analyses. In the first-line setting with FOLFOX, a 10%-13% difference in the estimated event-free rates was only observed around the 1-year endpoint while in the second-line setting with FOLFIRI, a 7%-15% difference was observed over the first 40 weeks only.

None of the studies showed a statistically significant effect on overall survival favourable to the addition of panitumumab in patients with wild-type KRAS tumours.

- Uncertainty in the knowledge about the beneficial effects

None of the studies showed a statistically significant effect of panitumumab on overall survival in patients with wild-type KRAS tumours. The objective tumour response to panitumumab was marginal in first-line treatment (55% vs. 48%), although slightly improved in the final analysis (57% vs. 48%), and only significant in second-line treatment (35% vs. 10%). The clinical relevance of response rate in this disease setting has not been established for this type of agent.

In the first-line setting (study 20050203):

- The findings lack internal consistency insofar as the differences in PFS and OS in patients with wild-type KRAS tumours are entirely driven by the ROW population, i.e. Central-Eastern Europe/Latin America/South Africa.
- There is also no evidence of benefit on PFS in patients older than 75 years or even in the large subpopulation of patients older than 65 years. Furthermore, in the very small group of elderly patients ≥ 75 years old there was a higher number of deaths, likely due to increased susceptibility to the toxicity of the combined regimen as reflected in the safety data. Any extrapolation of benefit to this population, which currently represents 40% of the patients with mCRC at diagnosis, is therefore impossible.
- Adding panitumumab to FOLFOX appears harmful in patients with an ECOG score of 2, where significantly shortened PFS and OS as well as increased toxicity were observed.

In the second-line setting (study 20050181):

- The highly statistical results shown in the primary PFS analysis ($p < 0.004$) are not considered robust in a more mature analysis, where they become borderline to the threshold level ($p< 0.01$) requested in the statistical analysis plan.
- A certain level of inconsistency was noted in the results. Importantly, no OS benefit was reported in the small group of patients older than 75 years (HR > 1). Even in the largest group of patients aged < 65 years, an apparent benefit in PFS (HR=0.69) did not translate into

OS benefit (HR = 0.92); the overall mortality rates were similar (66% vs. 65%), especially because of more deaths due to disease progression in the long-term follow-up (63% vs. 57% with FOLFIRI alone) (data from FU2 029.1).

Patient reported outcomes can be important especially given the high toxicity of the combined regimens. The various analyses of QoL data do not show any benefit of adding panitumumab but rather a numerical trend in favour of chemotherapy alone. This result is supported by a higher proportion of WT patients with a deterioration of their ECOG score in the FOLFIRI trial. These observations add uncertainties about any possible benefits of panitumumab in the claimed indications,

Finally, the uncertainties about the effects of anti-EGFR therapies on wild-type KRAS tumours are expected since it is now known that a number of other mutations in the signalling pathway may confer resistance to these therapies. Other biomarkers such as BRAF, PIK3CA/PTEN, or NRAS but also EGFR gene copy number, EGFR ligands (epiregulin and amphiregulin), single nucleotide polymorphisms in codon 497 of EGFR, or levels of EGFR downstream signalling phosphoproteins (e.g. pMEK1, pP70S6K) may increase predictive power for response to treatment and are awaiting validation in clinical trials.

Risks

- Unfavourable effects

In patients with mutant KRAS tumours, a clear negative impact of panitumumab was observed on time to progression, PFS and OS when it was combined with oxaliplatin-based chemotherapy in the first-line setting. These results were robust and found in both geographic regions. In contrast, the combination of panitumumab with FOLFIRI did not appear harmful in these patients, and thus, this negative effect seemed to be specific to oxaliplatin-based chemotherapy. The MAH hypothesised that this was due to a negative interaction between anti-EGFR antibodies and oxaliplatin in patients with mutant KRAS mCRC.

The addition of panitumumab did substantially increase the overall incidence of the high-grade AEs reported (i.e. grade ≥3, serious, or leading to treatment discontinuation). The patient incidence of grade ≥ 3 AEs was augmented from 76% to 88% with oxaliplatin and from 56% to 75% with irinotecan. This was due mainly to an increase in incidence/severity of diarrhoea, a well-known ADR of oxaliplatin and irinotecan, as well as to the added contribution of the toxicities specific to EGFR inhibitors.

- The occurrence of *diarrhoea* with panitumumab was higher than on chemotherapy alone, especially the most severe cases (with patient incidence increasing from 9% up to 14-18%) and serious cases (from 3-4% up to 10%; one fatal case). This was associated with an increased proportion of patients presenting with hypokalaemia and dehydration.
- Grade ≥3 *skin toxicities* were observed in 34% of the patients treated with panitumumab vs. 2% on chemotherapy alone. This included in particular severe (grade 3/4) rash and acneiform dermatitis, the occurrence of which rose with treatment duration.
- *Hypomagnesaemia*, sometimes associated with hypocalcaemia, also contributed to the excess toxicity of the combination of panitumumab with chemotherapy, as reflected by severe (grade ≥3) decreases in magnesium levels in 11% of the patients.
- Panitumumab also seemed to increase the incidence of *thromboembolism*, including severe cases (from 7% to 11% with oxaliplatin).

- Even general toxicities including fatigue/asthenia, anorexia and decreased weight were reported more frequently by patients receiving panitumumab than chemotherapy alone. A new ADR of Palmar-Plantar Erythrodysesthesia (PPE) syndrome was identified.

Importantly, all these effects of panitumumab, and especially diarrhoea and rash, had an impact on compliance with chemotherapy and its intensity in a significant number of cases with permanent discontinuation or dose delays and adjustments.

Elderly patients were in general more susceptible to chemotherapy toxicities, as could be observed to some extent in the control groups, but serious adverse events were more common in patients aged ≥ 65 years than in younger patients when panitumumab was added to chemotherapy. Some toxicities of panitumumab appeared particularly more frequent in patients older than 65 years; these mainly included diarrhoea, thromboembolic events, stomatitis/oral mucositis, and hypomagnesaemia.

- Uncertainty in the knowledge about the unfavourable effects

In study 20050181, the reporting rates of severe and serious AEs were about 20% lower in the ROW region (essentially Central-Eastern Europe), which provided 39% of the total population, than in the Western Europe/US/Australia region. This finding was attributed by the MAH to 'regional and cultural differences' but is still largely unexplained.

Fatal adverse events occurred at a similar rate in the treatment arms of the wild-type KRAS groups of both studies. In the mutant KRAS groups, increases in fatal adverse events with panitumumab were seen to some extent in both studies: 8% vs. 3% in the control arm of study 20050203 and 7% vs. 5% in the control arm of study 20050181. Recent analyses of the timing and cause of deaths in study 20050203 did not identify obvious toxicities to explain the mortality that was not related to disease progression. There was no clear signal for worse cardiac toxicity but a marginal increase cannot be ruled out.

The MAH argued that toxicity of panitumumab is manageable. However, severe protracted diarrhoea and disfiguring or painful skin lesions may be severely disabling with patients eventually being homebound. The impact of these toxicities on the patient quality of life was reflected by the absence of improvement with the addition of panitumumab and rather a numerical trend favouring chemotherapy alone. Furthermore, a higher proportion of patients exhibited a deterioration of their ECOG score in the FOLFIRI trial.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The difference in PFS was small and did not translate into significant improvement in OS or other clinical benefit.

The lack of evidence of QoL benefit over chemotherapy alone with a numerical trend in favour of chemotherapy alone and more frequent deterioration of ECOG performance status in the second-line setting is to be expected given the substantial increase in toxicity of the combination of panitumumab with chemotherapy as compared with chemotherapy alone. This is especially a concern in the older patients.

Given that KRAS determination is critical for the indication of panitumumab, it is questionable whether the small benefits achieved in clinical trials where KRAS status was centrally diagnosed can be generalised. Indeed, they are likely to be smaller in a broad clinical setting, where the reliability of KRAS diagnosis has not yet been established.

The negative impact of panitumumab on the survival of patients with KRAS mutant tumours when combined with oxaliplatin-based chemotherapy is considered a major concern since the proportion of patients with KRAS mutations potentially treated with panitumumab is unknown and very difficult to estimate. The reasons for such wrong treatments are multiple and include non evaluable test results, unreliable test methods, or mutations not detectable by the test used. Moreover, no clear reason has been found to explain this negative impact. No obvious toxic interaction has been found and it is not clear whether the negative effect is to be related to the mutant KRAS status only, or if there are other groups of patients at risk of negative effects, such as those with poor performance status. The MAH hypothesised that this is due to a negative interaction between anti-EGFR antibodies and oxaliplatin in patients with mutant KRAS mCRC.

- Benefit-risk balance

The modest increase in PFS observed in patients with wild-type KRAS tumours by the addition of panitumumab to the first and second line of chemotherapy for mCRC was not considered sufficient to outweigh the increased toxicity of the combinations.

Conclusion

On 17 March 2011 the CHMP considered this Type II variation not to be acceptable on the following grounds:

- The benefit in terms of progression free survival in the target population with wild-type KRAS tumours is modest. No effect could be observed in elderly patients and a detrimental effect was observed in patients with ECOG performance status of 2 in some of the subgroup analyses. No statistically significant difference was observed for overall survival. No benefit has been established in terms of other clinical endpoints such as Quality of Life
- The add-on toxicity of panitumumab is clinically significant with substantial increase in the rate of SAEs and grade ≥ 3 events. These concerns are heightened in elderly patients, as some toxicities of panitumumab appear particularly more frequent in these patients
- There is uncertainty about the current reliability of KRAS testing in clinical practice, which raises a concern since a detrimental effect on progression-free and overall survival has been reported in patients with mutant KRAS tumours for the combination of panitumumab with FOLFOX
- The modest increase in PFS observed in patients with wild-type KRAS tumours by the addition of panitumumab to the first and second line of chemotherapy for mCRC is not considered sufficient to outweigh the increased toxicity of the combinations

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group-Oncology that unanimously expressed a positive opinion towards the positive benefit/risk of the requested indications (combination with FOLFOX-first line indication and the combination with FOLFIRI–second line indication).

The Committee noted that although the improvement in median PFS was modest, it is within the same magnitude as that seen with other biological agents added to chemotherapy in both first and second line treatment and that the addition of anti-EGFR antibodies to chemotherapy in these disease settings is established in clinical practice in the EU. Especially in second line treatment (combination with FOLFIRI) the observed effect may be of higher clinical relevance given the poorer health status and worse prognosis of patients in this setting.

The lack of support by statistically significant improvements of OS could indeed be attributed to subsequent anti-EGFR therapy which was higher in the control arms of both studies (25.4% vs 12.9% with panitumumab add-on in patients with wild-type KRAS tumours in the first line FOLFOX study [Table 6] and 34.4% vs 12.5%, respectively, in the same population in the second line FOLFIRI study [Table 11]). The fact that patients in the control arms of the panitumumab studies were likely to cross over and receive subsequent anti-EGFR therapy once out of the studies and that this cross-over was higher in these later panitumumab studies compared to earlier cetuximab ones, may be seen as an indicator that the addition of anti-EGFR antibodies to chemotherapy for mCRC has been increasing.

Although the clinical relevance of ORR may not have been established for this type of agent in first and second line treatment of mCRC, the observed improvement cannot be ignored and it can be of clinical relevance in the first line setting, as a response (tumour shrinkage) may render the tumour resectable and thus allow surgical resection of metastases in certain cases, which may significantly prolong survival of patients eligible for this resection.

With regard to the inferior (in some instances numerically worse) results observed in elderly patients and patients with poor ECOG Performance Status (ECOG PS 2), the CHMP considered that indeed the numbers of patients in the relevant subgroups of the two studies are small and that the relevant post-hoc subgroup analyses should be interpreted with caution. It was therefore not considered appropriate to restrict any potential indication based on age or performance status. It is already clinical reality and it is reinforced via adequate warnings and precautions in the Product Information that decisions to use panitumumab in combination with chemotherapy in mCRC are based on clinical judgement which takes into account individual patient characteristics, including performance status and age. Furthermore, skin rash in the course of panitumumab treatment may be used to guide clinical decision making, although no strict recommendations can be given at present. No additional analyses were presented by the MAH on the potential value of skin rash as a predictive marker of benefit from panitumumab, as proposed by the SAG-O, but the MAH confirmed during the Oral Explanation that no skin rash was observed in patients receiving chemotherapy only, other than the Palmar-Plantar Erythrodysaesthesia (or hand-foot) Syndrome, as expected during treatment with fluoropyrimidines.

In terms of Quality of Life, the CHMP noted that, although an improvement in this would have been desirable, QoL was by and large unaffected by the addition of panitumumab to chemotherapy, even so in patients experiencing the common skin rash and diarrhoea. Moreover, the Committee was reassured by clinical experts' affirmations that toxicity of panitumumab was indeed manageable and that there is experience in handling panitumumab toxicity in clinical practice. With regard to elderly patients, who tended to show increased toxicity, it was confirmed that it is usual clinical practice for this type of anti-cancer agents to exercise expert clinical judgement in deciding who should receive panitumumab add-on taking into account performance status and other clinical considerations (disease burden, comorbidities etc).

Panitumumab should only be used in patients with wild-type KRAS tumour status and it should not be used in patients with mutant KRAS tumour status or in patients who have not been tested. The Committee was reassured that the KRAS testing methods were widely available and used in clinical practice, that the methods are robust and adequately sensitive and specific, at least as much as other established diagnostic methods such as HER2 and EGFR testing. In considering the SAG-O outcome the CHMP decided to contraindicate the combination of Vectibix with FOLFOX in patients with mutant *KRAS* mCRC or patients whose KRAS tumour status is unnown. Moreover, the risk of administering panitumumab to mutant KRAS tumour patients can be adequately managed via the agreed risk management plan (please refer to Risk Management Plan below).

With regard to biomarkers other than KRAS, the CHMP agreed that the level of EGFR expression does not play a major role in CRC in contrast to non-small cell lung cancer (NSCLC) and squamous cell

cancer of the head and neck (SCCHN), in which mean expression levels of EGFR are much higher and there is much larger inter-tumour variability. The CHMP stressed the importance of attempts to identify such biomarkers that could potentially help better the target population of panitumumab.

In conclusion, the CHMP considered after reviewing the additional subgroup efficacy analyses provided by the MAH and considering the expert advice received from the SAG-Oncology, that there is sufficient reassurance that the toxicity observed for panitumumab in combination with FOLFOX as first line treatment of patients with mCRC and in combination with FOLFIRI as second line treatment is manageable and no longer constitutes a major issue. It was confirmed by the experts, for example, that careful monitoring of skin toxicity is an established practice, which can be used to guide clinical decision making. Overall, the efficacy was considered to be clinically relevant in the applied doses and schedules of the specific combinations and very consistent with the known effect of other drugs with similar mechanism of action used in the same clinical setting. However, these conclusions cannot be considered to apply in general to other chemotherapy combinations. The product information has been amended to adequately reflect these restrictions.

The CHMP also acknowledged that in line with the advice received from the expert group, subgroup-specific trial mortality results cannot provide a reliable basis for individualising patient care, due to the play of chance. Thus, the CHMP concluded that the results in poor performance status and older age subgroups should be interpreted more cautiously as they may lead to a significant number of patients being left untreated inappropriately. Sufficient reassurance was provided from the expert group that clinical decisions can be sufficiently informed by the available data to allow adequate patient selection and management of toxicity depending on the clinical characteristics of the patients. Overall, the apparent lack of consistency in light of the unfavourable results seen in elderly and poor health status subgroups was no longer considered a major concern.

The CHMP was also reassured that KRAS testing is widely available in clinical practice and that its operational characteristics are adequate and well defined. The product information was amended on this issue and, most prominently, a contraindication was added on the use of panitumumab in combination with oxaliplatin-containing chemotherapy in patients with mutant KRAS tumour status or for whom KRAS status is unknown. Moreover, the agreed risk management plan and the additional risk minimisation activities in the form of physician educational materials can adequately manage the risk of treating with panitumumab patients with mutant KRAS tumours or patients whose KRAS tumour status is unknown, so that this risk was sufficiently low as not to pose a major concern. Finally, the CHMP agreed on the wording of a Direct Healthcare Professional Communication (please refer to Attachment 13) to be circulated to prescribers prior to the start of use of Vectibix with the aim to raise awareness on the issue of KRAS testing and its role during treatment with panitumumab.

Taking all these considerations into account, the CHMP revised its initial opinion and concluded that the benefit-risk balance of panitumumab in combination with FOLFOX as first line treatment of patients with mCRC and in combination with FOLFIRI as second line treatment of patients with mCRC who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) for their disease was positive.

3.30. Xarelto

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for stroke. It is estimated to currently affect over 6 million patients

in Europe. The prevalence of AF increases with age, being less than 1% among people under 60 years of age with estimates of more than 6% among those over 80 years of age.

Atrial fibrillation predisposes patients to a greater risk of stroke as a result of cardiogenic embolism. In the absence of treatment, patients with non-valvular AF have a 2- to 7-fold higher incidence of ischemic stroke than age-matched controls without AF.

There is general international agreement that recommend VKA therapy for patients with AF with any high risk factor and for those with more than 1 moderate risk factor. High risk factors are previous stroke, transient ischemic attack (TIA) or embolism, mitral stenosis, and prosthetic heart valve. Moderate risk factors are age ≥75 years, hypertension, heart failure and/or left ventricular ejection fraction ≤35% and diabetes mellitus.

The management of warfarin therapy can be challenging. Dietary changes, concomitant medications, herbal products, concomitant illness and other factors may influence a patient's response to warfarin. Therefore, maintaining INR within the target therapeutic range may be difficult in some patients, requiring frequent laboratory or point of care monitoring and dose adaptations.

Thus, there is an unmet medical need for alternative oral anticoagulants that can be given at fixed doses without the need for laboratory monitoring, that are as effective as warfarin in reducing the risk of stroke and systemic embolism, and that have an acceptable risk of bleeding as well as overall safety profile.

Beneficial effects

This application is primarily supported by one large pivotal study, which was an adequately designed double blind non-inferiority/superiority study with appropriate inclusion and exclusion criteria and an appropriate comparator of VKA treatment. The study population is judged to be representative for the European target population. The primary efficacy endpoint was the composite of stroke and non-CNS systemic embolism. There were 188 of 6958 subjects in the rivaroxaban group and 241 of 7004 subjects in the warfarin group who experienced an endpoint event corresponding in the primary non-inferiority analysis to a HR of 0.79 (95%CI 0.66, 0.96, $p<0.001$. Superiority was primarily claimed for rivaroxaban for the primary efficacy endpoint (HR 0.79, 95% CI 0.65, 0.95, $p<0.015$), however, this was based on an analysis of patients on treatment. An appropriate superiority analysis should be based on the ITT population and in these analyses superiority was not demonstrated. Thus, claims for superior efficacy as compared with VKA treatment should not be accepted. This conclusion is supported by the overall somewhat low TTR values which probably were due to the inclusion of some investigational centers with less experience in VKA treatment.

The outcome of the secondary end-points supports the primary analysis. For the two major secondary efficacy endpoints tested hierarchically according to the prospectively defined analysis plan (composite of stroke, non-CNS systemic embolism, vascular death and composite of stroke, non-CNS systemic embolism, vascular death and MI) superiority was shown for rivaroxaban in an analysis based on patients on treatment. Superiority was not demonstrated in a conventional superiority analysis based on the ITT population.

For the third predefined secondary efficacy analysis, all cause mortality, a rather strong numerical trend in favour of rivaroxaban with 208/7061 vs 250/7082 events corresponding to a HR of 0.85 (95% CI; 0.70, 1.02, p=0.073).

The performed sensitivity analyses supported the primary analysis.

There was a clear numerical difference with regard to haemorrhagic strokes and fatal haemorrhagic strokes in favour of rivaroxaban.

The overall efficacy results were essentially consistent in important subgroups, such as different age categories, different CHADS2 scores, subgroups with different degrees of renal impairment and concomitant diseases. The results in centers with different mean time in therapeutic range for VKA treatment was consistent with the overall results.

Uncertainty in the knowledge about the beneficial effects

An important source of uncertainty is derived from the imbalance in stroke rates during the one month's follow-up period as it demonstrates the importance for appropriate recommendations for how to switch to VKA treatment. Such improved recommendations have now been implemented in the SPC. The compiled data do not support the possibility of a rebound phenomenon, however, some uncertainty on this remains for the time being.

Risks

Unfavourable effects

The size of the safety database should be sufficient for a reasonable assessment of the safety profile of the product. Overall mortality rates were numerically lower in the rivaroxaban group (4.9% vs. 5.7%)

The incidences of major and clinically relevant bleedings were approximately similar between the treatment groups (5.4% in both groups) for major bleedings, but rates of critical organ bleedings and death related to bleedings were lower in the rivaroxaban group. The difference in the incidences of intracranial bleedings is of potential interest with the well-known bad prognosis in these patients when on warfarin (55/7111 vs. 84/7125 in the rivaroxaban and warfarin groups, from study 11630 respectively).

However, haemoglobin/hematocrit drop and transfusions were more common as was discontinuation due to bleeding in the rivaroxaban group. This, together with the reported higher incidences of mucosal bleedings among rivaroxaban treated patients (GI bleeding, haematuria, epistaxis, gingival bleeding) indicate a probable difference in bleeding pattern between the two anticoagulants. This has been acknowledged and discussed by the MAH. This important point was adequately described in the SPC,

A higher incidence of major and clinically relevant bleedings was seen among the rivaroxaban treated elderly patients as compared to the warfarin treated (26 vs. 23%, respectively). This was shown to be due to mucosal bleedings to a large extent and these observation underlines the importance of close clinical surveillance.

It is also of concern that in centers with better INR control major and clinically relevant bleedings were significantly more common in the rivaroxaban group. The bleeding pattern in these centers does not differ from the overall pattern. Males treated with rivaroxaban had somewhat more bleedings than those treated with warfarin while the opposite trend was observed for women. There is no obvious explanation for this and the differences may have been due to chance.

Hepatic adverse events were intensively monitored in the phase III studies. There are no indications in the provided data that rivaroxaban treatment would be associated with an increased risk for hepatic adverse events.

Unexpectedly, the incidence of cholelithiasis was higher in the rivaroxaban group. However in the compiled clinical documentation there is no clear indication for such an increased risk and the imbalance observe in the pivotal study may have been due to chance.

An imbalance in hypoglycaemic events disfavouring rivaroxaban (79 vs. 48) was reported. There are, however, no indications that rivaroxaban would exert a direct hypoglycaemic effect. The observation may partly be associated with a higher incidence of anaemia in the rivaroxaban group.

The incidence of other non-bleeding adverse events was similar in the 2 treatment groups.

Uncertainty in the knowledge about the unfavourable effects

Low haemoglobin/haematocrit levels were more commonly reported among the rivaroxaban treated patients. Haemoglobin values < 0.8 x baseline value were 604 in the rivaroxaban group as compared to 399 among the warfarin treated. Recommendations for clinical and laboratory monitoring for detection of occult bleedings should be implemented in the SPC.

Preliminary top-line results of the large "Magellan trial" for prevention of VTE in patients with an acute medical illness, population overlapping with the target SPAF population, has recently been submitted showing a disturbingly high bleeding incidence in the rivaroxaban arm. However, if the imbalance in bleeding observed in the heterogeneous population in the Magellan trial would reflect a true difference in bleeding tendency similar imbalances would have been expected in the large studies in other applications. Thus the differences seen in the Magellan trial may at least partially have been a chance finding.

Few premenopausal women were included in the AF studies. Genital bleeding was clearly more common among rivaroxaban treated women as compared to warfarin treated in the DVT studies. Appropriate precautionary measures were recommended in the SPC.

The lack of an antidote to recommend in case of severe bleeding events is a disadvantage as compared to the situation for warfarin. The MAH has provided updated information on their efforts to develop a specific antidote and a scientific advice is currently sought on the programme at the European level.

Balance

Importance of favourable and unfavourable effects

Currently, the only available treatment for prevention of systemic embolism in atrial fibrillation is VKA treatment from which long-standing experience exists. VKA treatment requires continuous monitoring and careful consideration of numerous possibilities for interaction with other drugs and food. The quality of VKA treatment is varying between centers and lower quality is associated with increased risks for bleeding and treatment failure. A simpler and more predictable alternative for oral use that would not need such intense monitoring would therefore be a potentially very valuable alternative, especially for patients where VKA treatment is not functioning well. This together with the demonstrated reduction in systemic embolism may represent important advantages for rivaroxaban treatment in atrial fibrillation.

A lower incidence in bleedings into critical organs, intracerebral bleedings, and fatal bleedings as compared to warfarin are also potential important advantages supported by a rather strong trend for overall lower mortality rates in the rivaroxaban group. However, treatment discontinuation due to bleeding, GI bleedings and bleedings from other mucosal sites were more common among the rivaroxaban treated patients. Thus, the bleeding pattern observed during rivaroxaban treated patients seems to differ from that observed during warfarin treatment. If patients are adequately monitored such bleedings may be clinically manageable and then less important in comparison with bleedings into critical organs and fatal bleedings.

Another potential advantage with rivaroxaban over warfarin is the lower potential for drug interactions.

Conclusions

The overall Benefit Risk of Xarelto was considered by the CHMP positive for the indication *"Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congwstive heart failure, hypertension, age ≥ years, diabetes mellitus, prior stroke or transient ischaemic attack".*