29 July 2011
EMA/CHMP/571474/2011
Patient Health Protection

**Monthly Report**

# Committee for Medicinal Products for Human Use (CHMP)

18 – 21 July 2011

## Centralised procedure

### *Initial applications for marketing authorisation*

### New medicines

The Committee adopted six positive opinions by consensus recommending the granting of marketing authorisations for the following new medicines:

- **Dexdor** (dexmedetomidine), from Orion Corporation, intended for sedation of adult intensive care unit (ICU) patients. Dexdor allows more flexibility in the ICU setting for patients who do not require deep sedation and has shown the additional advantage of reducing the time for extubation compared with the standard of care. The review for Dexdor began on 20 October 2010 with an active review time of 210 days.
- **Incivo** (telaprevir), from Janssen-Cilag International N.V., intended for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease. Telaprevir belongs to a new class of medicines for the treatment of chronic hepatitis that can directly inhibit viral replication in infected host cells which can lead to the eradication of the virus, and thus effectively to a cure of chronic hepatitis C. The CHMP assessed this application under an accelerated timetable, because it considered that, as 70% of hepatitis C virus infections in the Western world are genotype 1, there would be an important public health gain in making this medicine available to patients as a treatment option. The review for Incivo began on 19 January 2011 with an active review time of 150 days.
- **Mercaptopurine Nova Laboratories** (mercaptopurine monohydrate), an orphan medicine from Nova Laboratories Ltd, intended for the treatment of acute lymphoblastic leukaemia in adults, adolescents and children. The medicine has been formulated as a suspension, which provides better accuracy and ease of administration especially when used in small children. Development of an age-appropriate formulation to treat this disease was identified as a priority research area by

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

the Agency's Paediatric Committee. The review for Mercaptopurine Nova Laboratories began on 21 July 2010 with an active review time of 200 days.

- **Plenadren** (hydrocortisone), an orphan medicine from DuoCort Pharma AB, intended for the treatment of adrenal insufficiency in adults. The application dossier for Plenadren has been submitted as a 'hybrid application'. This means that the dossier contains administrative information, complete quality data, a clinical bioequivalence study with a reference medicine and non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature which can substitute or support certain tests or studies. The reference medicine for Plenadren is Hydrocortone. The review for Plenadren began on 23 June 2010 with an active review time of 210 days.
- **Vyndaqel** (tafamidis), from Pfizer Specialty UK Ltd, an orphan medicine intended for the treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy, a severe, progressive orphan disease. Vyndaqel is the first oral pharmacological treatment recommended for this rare disease. The CHMP recommended granting a marketing authorisation under exceptional circumstances because, due to the rarity of the disease, the applicant was not able to provide comprehensive evidence on the efficacy and safety of this medicine. The review for Vyndaqel began on 18 August 2010 with an active review time of 210 days.
- **Zytiga** (abiraterone acetate), from Janssen-Cilag International N.V., intended in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The CHMP assessed this application under an accelerated timetable, because it considered that the poor prognosis of the target patient population represents a high unmet medical need while the novel mechanism of action of abiraterone has the potential to offer an alternative therapeutic option for these patients. The review for Zytiga began on 19 January 2011 with an active review time of 150 days.

## Positive opinions for generic medicines adopted

The Committee adopted five positive opinions by consensus and six positive opinions by majority (Pioglitazone Accord, Pioglitazone ratiopharm, Pioglitazone ratiopharm GmbH, Pioglitazone ratio, Pioglitazone KrKa, Paglitaz) recommending the granting of marketing authorisations for the following generic medicines:

- **Levetiracetam Accord** (levetiracetam), from Accord Healthcare Ltd, intended for the treatment of partial onset seizures. Levetiracetam Accord is a generic of Keppra.
- **Levetiracetam Actavis** (levetiracetam), from Actavis Group PTC ehf, intended for the treatment of partial onset seizures. Levetiracetam Actavis is a generic of Keppra.
- **Matever** (levetiracetam), from Pharmathen S.A., intended for the treatment of partial onset seizures. Matever is a generic of Keppra.
- **Pioglitazone Accord** (pioglitazone hydrochloride), from Accord Healthcare Ltd, intended for the treatment of type 2 diabetes mellitus. Pioglitazone Accord is a generic of Actos.
- **Pioglitazone ratiopharm** (pioglitazone), from ratiopharm GmbH, intended for the treatment of type 2 diabetes mellitus. Pioglitazone ratiopharm is a generic of Actos.
- **Pioglitazone ratiopharm GmbH** (pioglitazone), from ratiopharm GmbH, intended for the treatment of type 2 diabetes mellitus. Pioglitazone ratiopharm GmbH is a generic of Actos.

- **Pioglitazone ratio** (pioglitazone), from ratiopharm GmbH, intended for the treatment of type 2 diabetes mellitus. Pioglitazone ratio is a generic of Actos.
- **Paglitaz** (pioglitazone), from Krka d.d. Novo mesto, intended for the treatment of type 2 diabetes mellitus. Paglitaz is a generic of Actos.
- **Pioglitazone Krka** (pioglitazone), from Krka d.d. Novo mesto, intended for the treatment of type 2 diabetes mellitus. Pioglitazone Krka is a generic of Actos.
- **Pramipexole Accord** (pramipexole), from Accord Healthcare Ltd, intended for the treatment of Parkinson's disease and restless legs syndrome. Pramipexole Accord is a generic of Mirapexin.
- **Telmisartan Teva Pharma** (telmisartan), from Teva Pharma B.V., intended for the treatment of essential hypertension in adults. Telmisartan Teva Pharma is a generic of Micardis.

*Summaries of opinion for these medicines are available on the Agency's website.*

## Negative opinion for new medicine adopted

The Committee adopted by majority a negative opinion recommending that no marketing authorisation should be granted for **Sumatriptan Galpharm** (sumatriptan), from Galpharm Healthcare Ltd. Sumatriptan Galpharm was intended as an over-the-counter medicine for the treatment of migraine attacks. Sumatriptan Galpharm is a generic of Imigran.

*More information about this opinion is available in a separate question-and-answer document on the Agency's website.*

## Withdrawals

The European Medicines Agency has been formally notified by Pfizer Limited of its decision to withdraw its application for an extension of the therapeutic indication for the centrally authorised medicine **Macugen** (pegaptanib sodium), 0.3 mg solution for injection. On 14 June 2010, Pfizer Limited submitted an application to extend the marketing authorisation for Macugen to include the treatment of visual impairment due to diabetic macular oedema in the indication. At the time of withdrawal, the application was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). Macugen was first authorised in the European Union on 31 January 2006. It is currently authorised for treatment of neovascular (wet) age-related macular degeneration. A separate question-and-answer document and press release with more information are available.

The European Medicines Agency has been formally notified by Sun Pharmaceutical Industries Europe B.V. of its decision to withdraw its application for a centralised marketing authorisation for the medicine **Doxorubicin SUN** (doxorubicin hydrochloride), 2 mg/ml concentrate for solution for infusion. Doxorubicin SUN was originally intended to be used for treatment of breast cancer, ovarian cancer, progressive myeloma and AIDS-related Kaposi's Sarcoma. The application for Doxorubicin SUN was assessed as a 'hybrid generic' of Caelyx. The application for the marketing authorisation for Doxorubicin SUN was submitted to the Agency on 5 February 2011. At the time of the withdrawal it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP).
A separate press release with more information is available.

## *Post-authorisation procedures*

## Positive opinions for extension of therapeutic indications adopted

The Committee adopted by consensus positive opinions for the following applications for extension of the therapeutic indications. This adds new treatment options for the following medicines that are already authorised in the EU:

- **Afinitor** (everolimus), from Novartis Europharm Ltd, to include treatment of patients with unresectable or metastatic, well- or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
- **Enbrel** (etanercept), from Wyeth Europa Ltd, to extend the lower age range in polyarticular juvenile idiopathic arthritis (JIA) from four to two years; and to extend the lower age range in paediatric plaque psoriasis from eight to six years.
- **Tarceva** (erlotinib), from Roche Registration Ltd, to include first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations.

*Summaries of opinion for these medicines, including their full therapeutic indications, are available on the Agency's website.*

## Negative opinions for extension of therapeutic indications adopted

The Committee adopted by majority negative opinions for **Ariclaim** (duloxetine), **Cymbalta** (duloxetine hydrochloride) and **Xeristar** (duloxetine hydrochloride), all from Eli Lilly Nederland B.V., recommending that the current therapeutic indications should not be extended to include the treatment of moderate to severe chronic somatic pain in patients not taking non-steroidal anti-inflammatory drugs (NSAIDs) regularly.

*More information about these opinions is available in a separate question-and-answer document on the Agency's website.*

## Additional safety information

The CHMP adopted by consensus changes to sections 4.4 and 4.8 of the SmPC of **Nplate** (romiplostim) from Amgen Limited, in order to include safety data available from a randomised clinical study of patients with thrombocytopenia associated with myelodysplastic syndrome (MDS) in which an increased risk of progression to acute myelogenous leukaemia (AML) was observed in patients treated with romiplostim compared to placebo. In addition, the key messages in the SmPC and Package Leaflet have been reinforced to highlight that a positive benefit-risk for romiplostim has only been established for the treatment of thrombocytopenia associated to chronic idiopathic thrombocytopenic purpura (ITP) and that romiplostim must not be used for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside clinical trials. The CHMP has endorsed a Direct Healthcare Professional Communication (DHPC) informing healthcare professionals of the revised recommendations.

Following a cumulative review of marketing authorisation holder's safety database and the published literature the CHMP adopted a positive opinion by consensus recommending a variation to the terms of the marketing authorisation for the medicinal product **Reyataz** (atazanavir sulphate) from Bristol-Myers Squibb Pharma EEIG. The SmPC was updated in sections 4.4 and 4.8 to include Stevens-Johnson syndrome, erythema multiforme, toxic skin eruptions, drug rash with eosinophilia and drug

rash with eosinophilia and systemic symptoms (DRESS) syndrome. The Package Leaflet has been amended accordingly.

As part of the assessment of the 5-year renewal application, the CHMP adopted by consensus amendments to sections 4.4 and 4.8 of the SmPC and Package Leaflet of **Sprycel** (dasatinib) from Bristol-Myers Squibb Pharma EEIG, with respect to Pulmonary Arterial Hypertension (PAH). PAH has been reported in association with dasatinib treatment in post-marketing reports. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. An echocardiography should be performed at treatment initiation in every patient presenting symptoms of cardiac disease and considered in patients with risk factors for cardiac or pulmonary disease. The Committee also agreed on a Direct Healthcare Professional Communication (DHPC).

The CHMP adopted by consensus the amendments to SmPC sections 4.4 and 4.5 of **Vfend** (voriconazole) from Pfizer Ltd to include a warning not to recommend the coadministration of everolimus and voriconazole. The Package Leaflet has been updated accordingly. This variation application was submitted following the CHMP assessment of a detected signal of suspected interactions and the already known interaction of everolimus with potent CYP3A4 inhibitors.

The CHMP adopted by consensus the amendments to SmPC sections 4.4 and 4.8 of **Advagraf** (tacrolimus) and **Modigraf** (tacrolimus) from Astellas Pharma Europe B.V. to include the occurrence of pure red cell aplasia (PRCA) in patients treated with tacrolimus. The Package Leaflet has been amended accordingly.

The CHMP has endorsed a Direct Healthcare Professional Communication (DHPC) letter for **MabThera** (rituximab) from Roche Registration Ltd which will be sent to healthcare professionals to alert them on fatal infusion-related reactions in patients with rheumatoid arthritis and noted that the changes to SmPC will be introduced accordingly.

# Other information on the centralised procedure

## *Update on Champix*

The Committee confirmed that the benefit-risk balance for Champix (varenicline) remains positive, despite the results of a recent meta-analysis of the medicine's side effects affecting the heart and blood vessels.

The Committee concluded that the slightly increased risk of cardiovascular events reported by the study's authors does not outweigh the benefits of Champix in helping people to stop smoking.

*More information about this review is available in a separate press release on the Agency's website.*

## *Advice on Vimpat agreed*

The CHMP agreed to a recall of Vimpat 15mg/ml syrup because of a quality defect in some batches leading to uneven distribution of the active substance lacosamide in the syrup. Doctors will be receiving a letter in the next few days advising them to contact their patients to switch them to Vimpat film coated tablets whenever possible.

*More information about this review is available in a separate press release and question-and-answer document on the Agency's website.*

## *Supply shortage of Thyrogen continues*

The Committee has been informed by Genzyme Europe B.V., the marketing authorisation holder for **Thyrogen** (thyrotropin alfa), that the supply shortage for this medicine will continue for longer than anticipated. When the Committee was initially informed of the supply shortage in March 2011, it was expected that it would be resolved by July 2011. However, the company now expects that supply of Thyrogen will continue to be restricted until 2012.

To deal with the ongoing shortage, the Committee has agreed with the company that doctors should be informed of revised temporary treatment recommendations:

- No new patients should be prescribed Thyrogen.
- In countries where Thyrogen is still available, supply should be prioritised for patients already scheduled and who are not able to tolerate thyroid hormone withdrawal, or in whom thyroid hormone withdrawal would not be effective.

Thyrogen is authorised for the diagnosis and treatment of thyroid tissue remnants post thyroidectomy in patients with thyroid cancer.

## *Lists of Questions*

The Committee adopted five Lists of Questions on initial applications (including two under the mandatory scope and three under the optional scope as per Regulation (EC) No. 726/2004), together with one List of Questions on a "line extension" application (in accordance with Annex I of Commission Regulation (EC) No. 1234/2008).

## *Detailed information on the centralised procedure*

Monthly figures related to the centralised procedure activities are published independently on the Agency's website within two weeks following the end of the CHMP meeting and can be found here. The overview of opinions for annual re-assessments and renewals is provided in **Annex 1**. The list of medicinal products for which marketing authorisations have been granted by the European Commission since the CHMP plenary meeting in May is provided in **Annex 2**.

## *Applications for marketing authorisation for orphan medicinal products*

Details of those orphan medicinal products that have been subject of a centralised application for marketing authorisation since the June 2011 CHMP plenary meeting are provided in **Annex 3**.

## *Name Review Group (NRG)*

Statistical information on the outcome of the checking of acceptability of proposed invented names for medicinal products processed through the centralised procedure is provided in **Annex 4**.

# Referral procedures

## Update on benefit-risk review of Multaq[1]

The Committee continued its benefit-risk review of Multaq to fully assess data from a clinical study (PALLAS) that show an increased risk of cardiovascular side effects such as cardiovascular death, stroke and cardiovascular hospitalisation in patients with permanent atrial fibrillation. Pending the outcome of the current review, prescribers in the European Union are reminded to follow the recommendations in the product information with respect to patients indicated for treatment, defined contraindications and warnings. Specifically, prescribers are advised to monitor patients regularly in order to ensure that they remain within the authorised indication and do not progress to permanent atrial fibrillation. Further advice will be issued at the time of the conclusion of the assessment in September.

*More information about this review is available in a separate press release on the Agency's website.*

## Review of pioglitazone-containing medicines concluded[2]

Finalising a benefit-risk review of **pioglitazone-containing medicines**, the CHMP confirmed that these medicines remain a valid treatment option for certain patients with type-2 diabetes but that there is a small increased risk of bladder cancer in patients taking these medicines. The CHMP concluded that this risk could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual patient's treatment.

Prescribers are advised not to use these medicines in patients with current or a history of bladder cancer and in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment.

*More information about this review is available in a separate press release and question-and-answer document on the Agency's website.*

## Review of Pandemrix concluded[3]

Finalising its review of **Pandemrix** and narcolepsy, the Committee recommended that in persons under 20 years of age the vaccine may only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed (e.g. in persons at risk of the complications of infection). The Committee confirmed that overall the benefit-risk balance of Pandemrix remains positive.

*More information about this review is available in a separate press release and question-and-answer document on the Agency's website.*

## Harmonisation referral concluded[4]

The Committee recommended harmonisation of the prescribing information for **Norvasc** (amlodipine besilate) and associated names, from Pfizer group of companies.

[1] The review of Multaq is being conducted in the context of a formal review under Article 20 of Regulation (EC) No 726/2004.
[2] The review of pioglitazone-containing medicines was conducted in the context of a formal review under Article 20 of Regulation (EC) No 726/2004.
[3] The review of Pandemrix was conducted in the context of a formal review under Article 20 of Regulation (EC) No 726/2004.
[4] The harmonisation referral on Norvasc was conducted under Article 30 of Directive 2001/83/EC, as amended.

This medicine is a calcium channel blocker used to treat hypertension, chronic stable angina and vasospastic or Prinzmetal's angina.

This review was initiated because of differences in the summaries of product characteristics, labelling and package leaflets in the EU Member States where this product is marketed.

*More information about this review is available in a separate question-and-answer document on the Agency's website.*

## Arbitration procedure concluded[5]

The Committee completed an arbitration procedure initiated by Malta because of a disagreement among EU Member States regarding the authorisation of the generic medicine **Dexamethasone Alapis** (dexamethasone), from Alapis S.A. This medicine is an anti-inflammatory, immunosuppressant agent.

This procedure was initiated because of Germany's concerns that the bibliography referring to dexamethasone tablets is not considered relevant with respect to Dexamethasone Alapis oral solution, due to the fact that the submitted literature data mainly concerned tablets and that no bridging data had been provided to justify the extrapolation of the published data on the efficacy and safety of dexamethasone tablets to Dexamethasone Alapis 0.4 mg/ml oral solution.

The Committee concluded that the data submitted were sufficient to show that Dexamethasone Alapis could be used safely and effectively, based on the well-established use of dexamethasone. The CHMP concluded that the benefits of Dexamethasone Alapis outweigh its risks, and therefore the marketing authorisation for Dexamethasone Alapis should be granted in Malta and all concerned Member States.

*More information about this review is available in a separate question-and-answer document on the Agency's website.*

## Review of ketoconazole-containing medicines for oral use started[6]

The Committee has begun looking at the benefit-risk balance of **ketoconazole-containing medicines** for oral use.

The review was initiated by France following concerns over the benefit-risk balance of ketoconazole-containing medicines as antifungal treatment due to the risk of hepatotoxicity and concerns that the efficacy is no longer considered as outweighing the risks.

The CHMP will now review all available data to assess the balance of benefits and risks of these medicines.

## Review of tolperisone-containing medicines started[7]

The Committee has begun looking at the benefit-risk balance of **tolperisone-containing medicines**, currently used as treatment of painful muscles spasms and spasticity.

The review was triggered by Germany following concerns over the benefit-risk balance of tolperisone-containing medicines due to a lack of evidence of efficacy in the currently approved indications and a

[5] Review of Dexamethasone Alapis was conducted in the context of a formal review under Article 29 of Directive 2001/83/EC.
[6] The review of ketoconazole-containing medicines is being conducted under Article 31 of Directive 2001/83/EC, as amended.
[7] The review of tolperisone-containing medicines is being conducted under Article 31 of Directive 2001/83/EC, as amended.

low safety profile with known risk of gastrointestinal and nervous system disorders and an increased reporting of hypersensitivity reactions.

The CHMP will now review all available data to assess the balance of benefits and risks of these medicines.

### Review of Octagam and associated names started[8]

The German national authority, Paul-Ehrlich Institut (PEI), has asked the Committee for opinion on the re-processing of certain batches of **Octagam** (human normal immunoglobulin 5% and 10%) and associated names. This review will result in a CHMP scientific opinion, which will be made publicly accessible.

Octagam is an intravenous solution used to strengthen the body's immune system to lower the risk of infection in patients with a weakened immune system.

### Arbitration procedures started[9]

The Committee initiated two arbitration procedures for **Yaz 24+4** (ethinylestradiol/drospirenone) and associated names and **Ethinylestradiol/drospirenon 24+4** (ethinylestradiol/drospirenone) and associated names from Bayer B.V., both indicated for female contraception. The procedures were initiated because of disagreements regarding the scientific evidence provided by the marketing authorisation holder to prove the safety and efficacy of the medicinal products in the applied indication.

## Mutual-recognition and decentralised procedures - Human

The CHMP noted the report from the 64th CMDh (Co-ordination Group for Mutual Recognition and Decentralised procedures-Human) held on 18-20 July 2011. For further details, please see the relevant press release on the CMDh website under the heading Press Releases: http://www.hma.eu/

## CHMP working parties

The CHMP was informed of the outcome of the discussions of the Scientific Advice Working Party (SAWP) meeting, which was held on 27-29 June 2011. For further details, please see **Annex 5**.

Documents adopted during the July 2011 CHMP meeting are listed in **Annex 6**.

## Upcoming meetings following the July 2011 CHMP plenary meeting

- The 80th meeting of the CHMP will be held at the Agency on 19-22 September 2011.
- The Name Review Group meeting will be held at the Agency on 22 September 2011.
- The 65th CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures) will be held at the Agency on 19-21 September 2011.

[8] The review of Octagam and associated names is being conducted in the context of a formal review under Article 5(3) of Regulation (EC) No 726/2004.
[9] The referral procedure for Yaz 24+4 (ethinylestradiol/drospirenone) and associated names and Ethinylestradiol/drospirenon 24+4 (ethinylestradiol/drospirenone) and associated names, initiated by Italy and Sweden, is being conducted under Article 6(12) of Commission Regulation (EC) No 1084/2003

# Organisational matters

The main topics addressed during the July 2011 CHMP meeting related to:

- The appointment of Mr Janne Komi as the new Finnish Alternate replacing Dr Kristiina Airola
- The adoption of Procedural Advice for CHMP on the need to convene a Scientific Advisory Group (SAG) or Ad Hoc Expert Meeting. The objective of this document is to provide procedural advice to Rapporteurs and CHMP members on timelines and factors for CHMP to consider when proposing whether to refer certain questions to a SAG or an Ad Hoc Expert Group. It will be available shortly on the Agency's website.

# Procedural Announcement

**IVIg monograph revision**

Following the recent increased rate of thromboembolic events seen with an intravenous immunoglobulin (IVIg) product, the Pharmacopoeia Commission has adopted a revised version of the monograph on Human normal immunoglobulin for intravenous administration (918). The production section was modified by adding "The method of preparation also includes a step or steps which have been shown to remove thrombosis generating agents. Emphasis is given to the identification of activated coagulation factors and their zymogens and process steps that may cause their activation. Consideration should also be given to other procoagulant agents which could be introduced by the manufacturing process." The proposed date of implementation for the revised 0918 monograph is 1 January 2012, subject to approval by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH). The monograph will be available on the EDQM website at the beginning of September to allow users to take the necessary actions until the implementation date.

Provided that the monograph revision is approved by CD-P-PH, a letter will be sent to all the relevant MAHs of centrally authorised products in September to inform them of the 0918 monograph changes, the required regulatory actions and timelines, and specific details of the requested analysis of pharmacovigilance data (see below).

Marketing Authorisation Holders (MAH) of human immunoglobulin products (normal and specific) for intravenous use should investigate their manufacturing process to determine if any change is required in order to comply with the revised 0918 monograph. If changes are required, they should submit the relevant variation (e.g. changes to the manufacturing process, in-process control and/or specification) with supporting validation data to update the marketing authorisation accordingly.

In case the manufacturing process already includes steps which have been shown to remove thrombosis generating agents, the relevant validation data will have to be submitted as a type II variation.

Furthermore, under the provisions of Art 16(2) of Reg 726/2004, an analysis of pharmacovigilance data for thromboembolic events will be requested.

Any signal of an increased rate of thromboembolic events or indications of thrombogenic (procoagulant) activity in a centrally authorised human immunoglobulin product (normal or specific) for intravenous administration should be immediately reported to EMA.

Noël Wathion
Head of Unit
Patient Health Protection, Tel. +44(0)20 74 18 85 92

This CHMP Monthly Report and other documents are available on the Internet at the following address: http://www.ema.europa.eu

# Annex 1 to CHMP Monthly Report July 2011

| Opinions for annual re-assessment applications | | |
|---|---|---|
| **Name of medicinal product (INN) MAH** | **Outcome** | **Comments** |
| **Prialt** (Ziconotide), Eisai Ltd. | Positive Opinion | Marketing Authorisation remains under exceptional circumstances |

| Opinion for renewals of conditional Marketing Authorisation | | |
|---|---|---|
| **Name of medicinal product (INN) MAH** | **Outcome** | **Comments** |
| N/A | | |

| Opinions for 5-Year Renewal applications | | |
|---|---|---|
| **Name of medicinal product (INN) MAH** | **Outcome** | **Comments** |
| **Sprycel** (Dasatinib), Bristol-Myers Squibb Pharma EEIG | Positive Opinion | Recommending additional renewal |
| **Elaprase** (Idursulfase), Shire Human Genetic Therapies AB | Positive Opinion | Recommending additional renewal |
| **Foscan** (Temoporfin), biolitec pharma ltd., | Positive Opinion | Unlimited validity |
| **BYETTA** (exenatide), Eli Lilly Nederland B.V. | Positive Opinion | Unlimited validity |
| **Suboxone** (Buprenorphine / Naloxone), RB Pharmaceuticals Ltd. | Positive Opinion | Unlimited validity |

| Accelerated Assessment Procedures | | | |
|---|---|---|---|
| **Substance (Chemical/Biological)** | **Intended Indication(s)** | **Accelerated Assessment Requests** | |
| | | Accepted | Rejected |
| N/A | | | |

# Annex 2 to CHMP Monthly Report July 2011

## *Medicinal products granted a community marketing authorisation under the centralised procedure since the June 2011 CHMP Monthly Report*

| **Invented name** | **Benlysta** |
|---|---|
| INN | belimumab |
| Marketing Authorisation Holder | Glaxo Group Limited |
| Proposed ATC code | L04AA26 |
| Indication | 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. |
| CHMP Opinion date | 19/05/2011 |
| Marketing Authorisation Date | 18/07/2011 |

| Invented name | **Fampyra** |
|---|---|
| INN | fampridine |
| Marketing Authorisation Holder | Biogen Idec Ltd |
| Proposed ATC code | N07XX07 |
| Indication | Improvement of walking in adult patients with multiple sclerosis with walking disability |
| CHMP Opinion date | 19/05/2011 |
| Marketing Authorisation Date | 20/07/2011 |

| Invented name | **TOBI Podhaler** |
|---|---|
| INN | Tobramycin |
| Marketing Authorisation Holder | Novartis Europharm Limited |
| Proposed ATC code | J01GB01 |
| Indication | Suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis |
| CHMP Opinion date | 14/04/2011 |
| Marketing Authorisation Date | 20/07/2011 |

| Invented name | **XGEVA** |
|---|---|
| INN | denosumab |
| Marketing Authorisation Holder | Amgen Europe B.V. |
| Proposed ATC code | M05BX04 |
| Indication | Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours |
| CHMP Opinion date | 19/05/2011 |
| Marketing Authorisation Date | 13/07/2011 |

| Invented name | **YERVOY** |
|---|---|
| INN | ipilimumab |
| Marketing Authorisation Holder | Bristol-Myers Squibb Pharma EEIG |
| Proposed ATC code | L01XC11 |
| Indication | Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy |
| CHMP Opinion date | 19/05/2011 |
| Marketing Authorisation Date | 13/07/2011 |

| Invented name | **Victrelis** |
|---|---|
| INN | boceprevir |
| Marketing Authorisation Holder | Merck Sharp & Dohme Ltd |
| Proposed ATC code | Not yet assigned |
| Indication | Treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy |
| CHMP Opinion date | 19/05/2011 |
| Marketing Authorisation Date | 18/07/2011 |

| Invented name | **Sprimeo HCT** |
|---|---|
| INN | Aliskiren/ hydrochlorothiazide |
| Marketing Authorisation Holder | Novartis Europharm Limited |
| Proposed ATC code | C09XA52 |
| Indication | Treatment of essential hypertension in adults |
| CHMP Opinion date | 17/02/2011 |
| Marketing Authorisation Date | 23/06/2011 |

# Annex 3 to CHMP Monthly Report July 2011

## *Overview of designated orphan medicinal products that have been the subject of a centralised application for marketing authorisation:*

Update since the June 2011 CHMP meeting

| Active substance | Invented name | Sponsor/applicant | EU designation number | Designated orphan indication |
|---|---|---|---|---|
| (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropane nitrile phosphate | Jakavi | Novartis Europharm Limited | EU/3/09/620 | Treatment of myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia |
| Idebenone | SAN Idebenone | Santhera Pharmaceuticals (Deutschland) GmbH | EU/3/07/434 | Treatment of Leber's hereditary optic neuropathy |
| Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E | Adcetris | Takeda Global Research and Development Centre (Europe) Ltd | EU/3/08/596 | Treatment of Hodgkin lymphoma |

# Annex 4 to CHMP Monthly Report July 2011

## NAME REVIEW GROUP (NRG)

| | NRG meeting 25 Jan 2011 | | NRG meeting 22 March 2011 | | NRG meeting 24 May 2011 | | NRG meeting 28 June 2011 | | NRG meeting 22 Sept 2011 | | NRG meeting 17 Nov 2011 | | 2011 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected |
| Proposed invented names | 34 | 68 | 56 | 50 | 59 | 41 | 56 | 55 | | | | | **205** | **214** |
| Justification for retention of invented name * | 0 | 2 | 4 | 6 | 2 | 4 | 4 | 0 | | | | | **10** | **12** |

*In case of objections to the proposed invented name(s), the applicant may justify the retention of the proposed invented name using the relevant justification form available on the EMEA website.

| | NRG meeting 25 Jan 2011 | | NRG meeting 22 March 2011 | | NRG meeting 24 May 2011 | | NRG meeting 28 June 2011 | | NRG meeting 22 Sept 2011 | | NRG meeting 17 Nov 2011 | | 2011 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Objections | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected | Accepted | Rejected |
| Total number of objections raised | 155 | 90 | 102 | 91 | 94 | 63 | 95 | 41 | | | | | **446** | **285** |
| **Criterion - Safety concerns** | | | | | | | | | | | | | | |
| Similarity with other Invented name | 125 | 73 | 82 | 74 | 48 | 53 | 87 | 26 | | | | | **342** | **226** |
| Conveys misleading therapeutic/pharmaceutical connotations | 2 | 3 | 0 | 1 | 1 | 0 | 1 | 1 | | | | | **4** | **5** |
| Misleading with respect to composition | 3 | 1 | 5 | 5 | 6 | 0 | 0 | 0 | | | | | **14** | **6** |
| **Criterion - INN concerns** | | | | | | | | | | | | | | |
| Similarity with INN | 8 | 6 | 5 | 2 | 4 | 1 | 3 | 0 | | | | | **20** | **9** |
| Inclusion of INN stem | 5 | 3 | 3 | 2 | 3 | 0 | 1 | 3 | | | | | **12** | **8** |
| **Criterion - Other public health concerns** | | | | | | | | | | | | | | |
| Unacceptable qualifiers | 1 | 0 | 3 | 2 | 2 | 0 | 0 | 1 | | | | | **6** | **3** |
| Conveys a promotional message | 1 | 0 | 2 | 5 | 0 | 8 | 3 | 1 | | | | | **6** | **14** |
| Appears offensive or has a bad connotation | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | | | | | **4** | **0** |
| Similarity between name of individual active substance and fixed combinations and/or between fixed combinations | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | | | | | **2** | **1** |
| Similarity between name of prodrug and related active substance | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | **0** | **0** |

See *Guideline on the Acceptability of Names for Human Medicinal Products Processed through the Centralised Procedure (CPMP/328/98 Rev. 5)* for detailed explanations of criteria used.

# Annex 5 to CHMP Monthly Report July 2011

## *Pre-authorisation: scientific advice and protocol assistance*
## *EMA centralised procedures*

| | 1995 - 2010 | 2011 | Overall total |
|---|---|---|---|
| Scientific Advice | 1368 | 163 | 1531 |
| Follow-up to Scientific Advice | 320 | 44 | 364 |
| Protocol Assistance | 297 | 30 | 327 |
| Follow-up to Protocol Assistance | 133 | 15 | 148 |
| | **2118** | **252** | **2370** |

| FDA Parallel Scientific Advice | 2006 - 2010 | 2011 | Overall total |
|---|---|---|---|
| Completed | 9 | 5 | 14 |
| Ongoing | 0 | 0 | 0 |
| Foreseen | 0 | 3 | 3 |
| | **9** | **8** | **17** |

## *Outcome of the July 2011 CHMP meeting in relation to scientific advice procedures*

### Final scientific advice procedures

| Substance | Intended indications(s) | Type of request | | | | Topic | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | New | | Follow-up | | Pharmaceutical | Pre-clinical | Clinical | Significant Benefit |
| | | SA | PA | SA | PA | | | | |
| Biological | Treatment of malabsorption due to exocrine pancreatic insufficiency. | | *x* | | | | *x* | *x* | |
| Biological | Treatment of diabetes mellitus. | *x* | | | | *x* | *x* | *x* | |
| Biological | Treatment of diabetes mellitus. | *x* | | | | *x* | *x* | *x* | |
| Biological | Treatment of severe hypoglycaemia. | *x* | | | | *x* | *x* | *x* | |
| Chemical | Treatment of opioid-induced constipation. | *x* | | | | *x* | *x* | *x* | |
| Advanced therapy | Treatment of Crohn's disease. | *x* | | | | | | *x* | |
| Biological | Treatment of growth hormone deficiency. | *x* | | | | *x* | *x* | *x* | |

| Substance | Intended indications(s) | Type of request | | | | Topic | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | New | | Follow-up | | Pharmaceutical | Pre-clinical | Clinical | Significant Benefit |
| | | SA | PA | SA | PA | | | | |
| Chemical | Treatment of post-operative gastro-intestinal motility disorders. | *x* | | | | | *x* | *x* | |
| Biological | Treatment of systemic lupus erythematosus. | *x* | | | | *x* | *x* | *x* | |
| Chemical | Treatment of non-small cell lung cancer. | *x* | | | | *x* | | *x* | |
| Chemical | Treatment of castrate-resistant prostate cancer. | | | *x* | | | *x* | | |
| Chemical | Treatment of familial adenomatous polyposis. | | | | *x* | | | *x* | |
| Biological | Treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis. | *x* | | | | *x* | *x* | *x* | |
| Biological | Treatment of Behçet's disease uveitis. | | *x* | | | | *x* | *x* | |
| Chemical/ Biological | Treatment of acute lymphoblastic leukemia. | *x* | | | | | | *x* | |
| Chemical | Treatment of acute myelogenous leukemia. | *x* | | | | | | *x* | |
| Chemical | Treatment of primary myelofibrosis. | | *x* | | | | *x* | | |
| Biological | Treatment of psoriasis. | *x* | | | | *x* | *x* | *x* | |
| Chemical | Treatment of endometrial carcinoma. | *x* | | | | *x* | *x* | *x* | |
| Chemical/ Biological | Treatment of HER2-positive breast cancer. | *x* | | | | *x* | | | |
| Chemical | Treatment of pulmonary arterial hypertension. | | | | *x* | *x* | *x* | *x* | *x* |
| Chemical | Treatment of thrombocytopenia. | *x* | | | | | | *x* | |
| Advanced therapy | Treatment of coronary artery disease. | *x* | | | | *x* | *x* | | |
| Chemical | Treatment of hypertension. | | | *x* | | | | *x* | |
| Chemical | Treatment of postmenopausal osteoporosis. | *x* | | | | | *x* | *x* | |
| Chemical | Treatment of osteoarthritis. | *x* | | | | | *x* | *x* | |
| Biological | Treatment of Alzheimer's disease. | *x* | | | | | *x* | *x* | |
| Chemical | Treatment of Alzheimer's disease. | | | *x* | | | | *x* | |
| Chemical | Treatment of chronic pain. | | | *x* | | *x* | | *x* | |

| Substance | Intended indications(s) | Type of request | | | | Topic | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | New | | Follow-up | | Pharmaceutical | Pre-clinical | Clinical | Significant Benefit |
| | | SA | PA | SA | PA | | | | |
| Biological | Treatment of amyotrophic lateral sclerosis. | | *x* | | | | *x* | *x* | *x* |
| Chemical | Treatment of schizophrenia. | | | *x* | | | | *x* | |
| Chemical | Treatment of partial-onset seizures. | *x* | | | | *x* | | *x* | |
| Chemical | Treatment of partial-onset seizures. | *x* | | | | | | *x* | |
| Chemical | Treatment of major depressive disorder. | *x* | | | | | *x* | *x* | |
| Chemical | Treatment of ADHD. | *x* | | | | | | *x* | |
| Chemical | Treatment of vasomotor symptoms. | *x* | | | | | *x* | *x* | |
| Chemical | Treatment of keratoconjunctivitis sicca. | *x* | | | | | | *x* | |
| Chemical | Treatment of age-related macular degeneration. | *x* | | | | *x* | | | |
| Biological | Treatment of postmenopausal osteoporosis. | *x* | | | | | *x* | *x* | |
| Chemical | Prophylaxis of endophthalmitis. | *x* | | | | *x* | *x* | *x* | |

**SA: scientific advice**
**PA: protocol assistance**

The above-mentioned 29 Scientific Advice letters, 4 Protocol Assistance letters, 5 Follow-up Scientific Advice and 2 Follow-up Protocol Assistance letters were adopted at the 18 – 21 July 2011 CHMP meeting.

## New requests for scientific advice procedures

The Committee accepted 30 new Requests for which the procedure started at the SAWP meeting held on 27 – 30 June 2011. The new requests are divided as follows: 17 Initial Scientific Advice, 10 Follow-up Scientific Advice, 1 Initial Protocol Assistance and 2 Follow-up Protocol Assistance.

# Annex 6 to CHMP Monthly Report July 2011

***Documents adopted during the July 2011 CHMP meeting***

## Biologics Working Party (BWP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/BWP/706271/2010 | Guideline on plasma-derived medicinal products | **adopted** |
| EMA/CHM/BWP/368186/2011 | Guideline on Quality Aspects on the Isolation of Candidate Influenza Vaccine Viruses in Cell Culture | **adopted** |

## Biosimilar Medicinal Product Working Party (BMWP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/BMWP/522386/2011 | Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins | **3-month public consultation** |
| EMA/CHMP/BMWP/506470/2011 | Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin | **3-month public consultation** |

## Blood Products Working Party (BP WP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/BPWP/144552/2009 | Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products | **adopted** |
| EMA/CHMP/BPWP/144533/2009 | Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products | **adopted** |

## Central Nervous System Working Party (CNS WP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/607022/2009 | Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)<br>• Comments received (EMA/71893/2011) | **adopted** |

[10] Adopted or released for consultation documents can be found at the European Medicines Agency website (under "Document library-Public Consultations" or under "Regulatory-Human Medicines").

## Pharmacokinetics Working Party (PKWP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMEA/CHMP/EWP/192217/2009 Rev.1 | Guideline on Bioanalytical Method Validation | **adopted** |
| EMA/CHMP/806058/2009 | Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product | **6-month public consultation** |

## Safety Working Party (SWP)

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/SWP/708666/2010 | Concept Paper on the need for revision of the Guideline on Non-Clinical Local Tolerance Testing of Medicinal Products CPMP/SWP/2145/00 | **3-month public consultation** |

## ICH

| Reference number | Document | Status[10] |
|---|---|---|
| EMA/CHMP/ICH/820/2003 | ICH guideline M2 - questions and answers | **adopted** |
| EMA/CHMP/ICH/507008/2011 | ICH guideline M3(R2) - questions and answers | **adopted** |
| EMA/CHMP/ICH/731268/1998 | ICH guideline S6(R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals | **adopted** |