30 November 2017
EMA/PRAC/782491/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 23 - 26 October 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006, Rev. 1).

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the 23-26 October 2017 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II – List of participants). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 23-26 October 2017

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Minutes of the previous meeting on 25-29 September 2017

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 25-29 September 2017 were published on the EMA website on 24 November 2017 (EMA/PRAC/782068/2017).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

2.1.1. Hydroxyethyl starch (HES)[1] (NAP) - EMEA/H/A-107i/1457

Applicants: Fresenius Kabi Deutschland GmbH (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin), Seruwerk Bernburg AG (Hesra); various

[1] Solution for infusion

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance following notification by Sweden of a referral under Article 107i of Directive 2001/83/EC, based on pharmacovigilance data

Background

Hydroxyethyl starch (HES) is a colloid indicated for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

The Swedish Medical Products Agency (MPA) sent a letter of notification dated 17/10/2017 along with a rationale for triggering a referral procedure under Article 107i of Directive 2001/83/EC for the review of HES-containing solutions further to the results of drug utilisation studies (DUS) requested by PRAC as a condition to their marketing authorisations in line with the conclusions of two previous referrals under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) respectively conducted by the PRAC in 2013 for those medicinal products. For further background, see PRAC minutes October 2013, PRAC minutes July 2014, PRAC minutes October 2014, PRAC minutes February 2015, PRAC minutes July 2015 and PRAC minutes October 2017. See also under 7.3.3.

Discussion

The PRAC noted the notification letter from the Swedish Medical Products Agency as well as its rationale and discussed three lists of questions (LoQ), namely for MAHs, an ad-hoc expert group, and for stakeholders, to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Patrick Batty as Rapporteur and Ulla Wändel Liminga as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/691228/2017) and a timetable for the procedure (EMA/PRAC/691227/2017). In addition, the PRAC adopted a LoQ (EMA/PRAC/691743/2017) to stakeholders[2] and a LoQ to an ad-hoc expert group meeting to be organised in December 2017.
- The PRAC discussed the option to conduct a public hearing in the context of the Article 107i procedure on medicinal products containing HES, according to the pre-defined criteria set out in the rules of procedure[3] (EMA/363479/2015). It was agreed by the Committee that, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

2.2. Ongoing procedures

None

[2] E.g. healthcare professionals, patients' organisations or general public
[3] Rules of procedure on the organisation and conduct of public hearings at the PRAC

2.3. Procedures for finalisation

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

3.1.1. Flupirtine (NAP) - EMEA/H/A-31/1458

Applicants: various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Martin Huber

Scope: Review of the benefit-risk balance following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

The German Medicines Agency[4] (BfArM) sent a letter of notification dated 19/10/2017 of a referral under Article 31 of Directive 2001/83/EC for the review of flupirtine-containing medicines used for short and long-term pain relief, further to the results of studies that were requested by PRAC to evaluate the effectiveness of the measures introduced by PRAC to restrict the use of these medicines due to concerns about liver problems as a conclusion of a previous referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-107i/1363) conducted by PRAC in 2013. For further background, see PRAC minutes March 2013, PRAC minutes May 2013, PRAC minutes June 2013, PRAC minutes May 2014, PRAC minutes June 2014, PRAC Minutes December 2014, PRAC minutes March 2015, PRAC minutes July 2015 and PRAC minutes March 2017. See also under 7.3.2.

Discussion

The PRAC noted the notification letter from the German Medicines Agency and discussed a list of questions (LoQ) to be addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Ana Sofia Martins as Rapporteur and Martin Huber as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs (EMA/PRAC/697552/2017) and a timetable for the procedure (EMA/PRAC/697898/2017).
- The PRAC discussed the option to conduct a public hearing in the context of the Article 31 procedure on medicinal products containing-flupirtine, according to the pre-defined criteria set out in the rules of procedure[5] (EMA/363479/2015). It was agreed by the Committee that at this stage in the assessment, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a

[4] Federal Institute for Drugs and Medical Devices
[5] Rules of procedure on the organisation and conduct of public hearings at the PRAC

public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

3.2. Ongoing procedures

3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

Scope: Review of the benefit-risk balance following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The ongoing review also assesses the need for adequate and consistent risk minimisation measures (RMMs) and the impact of this safety concern if confirmed on the overall benefit risk balance of quinolones and fluoroquinolones for systemic and inhalational use, especially in authorised indications which are related to treatment of non-serious/non severe infections. For further background, see PRAC minutes February 2017, PRAC minutes June 2017 and PRAC minutes October 2017.

Summary of recommendation(s)/conclusions

- The PRAC adopted a list of questions (LoQ) to the Infectious Disease Working Party (IDWP) organised on 23-24 November 2017.

3.3. Procedures for finalisation

3.3.1. Daclizumab - ZINBRYTA (CAP) – EMEA/H/A-20/1456

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia; PRAC Co-rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Zinbryta (daclizumab), conducted to investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product, is to be concluded. The review was initiated following cases of serious liver injury, including a fatal case of fulminant liver failure. In July 2017, the PRAC recommended provisional measures without prejudice to the final conclusions of the ongoing procedure. For further background and information on the provisional measures, see PRAC minutes June 2017, PRAC minutes July 2017, PRAC minutes September 2017 and PRAC minutes October 2017. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC reviewed the totality of the data provided by the MAH of Zinbryta (daclizumab), including at an oral explanation, on cases of serious liver injury reported since the initial marketing authorisation(s) and safety and efficacy data from clinical trials, in relation to the overall risk of liver injury with daclizumab. The PRAC also considered the views expressed by the scientific advisory group on neurology (SAG-N) held on 12 October 2017, presented to the PRAC at the current meeting, and discussed the conclusions reached by the Rapporteurs.

The PRAC concluded that daclizumab is associated, during treatment and for several months after the end of treatment, with an unpredictable and potentially fatal risk of immune-mediated liver injury. The PRAC noted that a fatal case had occurred despite the risk minimisation measures already implemented, including monthly liver function monitoring. The PRAC thus considered that further measures are needed to minimise this risk including limiting the use of the product to situations where no other therapeutic options are suitable.

As a consequence, the PRAC recommended restriction of the indication of daclizumab to the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment.

In addition, the PRAC recommended strengthening the current warnings to take into account that liver function, including bilirubin levels, of all patients should be monitored at least monthly, before each administration of daclizumab, and for six months after end of treatment, and stricter discontinuation criteria in case of elevated transaminase should now be applied. Discontinuation should also be considered if an adequate therapeutic response has not been achieved or if the liver function monitoring is not adhered to.

Furthermore, PRAC recommended that all patients are informed about signs or symptoms suggestive of liver dysfunction and promptly referred to a hepatologist in case of such signs or symptoms. In addition, prior to treatment initiation, patients should be screened for hepatitis B and C infection and initiation is not recommended in patients with other autoimmune conditions. Administration of daclizumab with other medicinal products of known hepatotoxic potential should be done with caution. The PRAC also considered it necessary to introduce an acknowledgement form to ensure patients have been adequately informed of the risks of liver injury associated with daclizumab. The educational material in place should also be updated.

The Committee considered that the benefit-risk balance of Zinbryta (daclizumab) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary[6] the terms of the marketing authorisation(s) for Zinbryta (daclizumab) to be considered by CHMP for an opinion – See EMA Press Release (EMA/707022/2017) entitled 'PRAC recommends further restrictions for multiple sclerosis medicine Zinbryta due to risk of serious liver damage'.
- The PRAC also agreed on the distribution of a direct healthcare professional communication (DHPC) and reviewed its content together with a communication plan.

Post-meeting note: the press release entitled 'EMA concludes review of Zinbryta and confirms further restrictions to reduce risk of liver damage' (EMA/733064/2017) representing the opinion adopted by the CHMP was published on the EMA website on 10 November 2017.

3.4. Re-examination procedures[7]

3.4.1. Paracetamol[8] (NAP); paracetamol, tramadol[9] (NAP) - EMEA/H/A-31/1445

Applicant(s): GlaxoSmithKline Consumer Healthcare AB (Alvedon 665 mg modified-release tablet), various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Adam Przybylkowski

Scope: Review of the benefit-risk balance of paracetamol modified release following notification by Sweden of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the September 2017 PRAC meeting[10], to suspend the marketing authorisations of modified release paracetamol- and paracetamol/tramadol-containing products, two MAHs concerned by this referral procedure requested a re-examination. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes February 2017, PRAC minutes March 2017, PRAC minutes July 2017, PRAC minutes September 2017 and PRAC minutes October 2017.

Discussion

At the organisational matters teleconference held on 9 November 2017, the PRAC noted the receipt of the grounds for re-examination from the two MAHs concerned by this referral procedure. The PRAC discussed the organisation of an ad-hoc expert group meeting in the course of the re-examination procedure[11], as well as a consolidated timetable for the procedure.

[6] Update of SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and Annex II-D. The package leaflet is updated accordingly
[7] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[8] Modified release formulations
[9] Modified release formulations
[10] Held on 29 August-1 September 2017
[11] Under Article 32 of Directive 2001/83/EC

Summary of recommendation(s)/conclusions

- On 20 November 2017, the Committee adopted by written procedure a list of questions (LoQ) and a list of experts (LoE) for the ad-hoc expert group meeting organised on 23 November 2017. The PRAC also adopted on 10 November 2017 a final timetable (EMA/PRAC/460935/2016 Rev.3) for the re-examination procedure.

3.5. Others

None

4. Signals assessment and prioritisation[12]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

4.2.1. Levonorgestrel[13] (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of arthralgia

EPITT 19109 – New signal

Lead Member State: DE

Background

Levonorgestrel is a progestogen indicated for contraception and treatment of menorrhagia as an intrauterine device (IUD).

As a conclusion of the PSUSA procedure PSUSA/00001856/201412 (see PRAC minutes September 2015), the MAH for Mirena and Jaydess (levonorgestrel-releasing IUD) was requested to closely monitor cases of arthralgia and breast discharge, as well as the possible interaction with lamotrigine, and to submit to relevant NCAs cumulative reviews within a year of finalisation of the PSUSA procedure. In the context of the evaluation of the cumulative reviews accordingly provided later, Germany (BfArM) requested PRAC advice on its assessment, proposed list of questions and request for additional data to be addressed by the MAH within 60 days with regards to the risk of arthralgia and the risk of breast discharge (see PRAC minutes July 2017).

Further to the responses provided by the MAH, a signal of arthralgia was identified by

[12] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

[13] Intrauterine device (IUD)

Germany. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence, including the data submitted by the MAH and an analysis performed in EudraVigilance, the PRAC agreed that the evidence does not support a causal association between the use of levonorgestrel-releasing intrauterine systems and arthralgia. The sudden increase in number of cases observed in EudraVigilance is geographically and temporally limited and probably represents a stimulated reporting. Therefore, the PRAC concurred that no further regulatory action is needed in light of current knowledge. Nevertheless, the MAHs for levonorgestrel-releasing IUD should continue to monitor arthralgia as part of routine safety surveillance.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for levonorgestrel-releasing intrauterine systems should continue to monitor arthralgia as part of routine safety surveillance.

4.3. Signals follow-up and prioritisation

4.3.1. Amitriptyline (NAP)

Applicant(s): various

PRAC Rapporteur: Agni Kapou

Scope: Signal of drug-induced liver injury (DILI) and hepatocellular injury

EPITT 18890 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAH for the originator of the amitriptyline-containing product replied to the request for information on the signal of drug-induced liver injury (DILI) and hepatocellular injury and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence including the patient exposure data provided as well as the available non-clinical, clinical, epidemiological and post-marketing data with regards to a possible association between amitriptyline treatment and DILI or hepatocellular injury, the PRAC agreed that the product information already includes sufficient terms to encompass these risks. Therefore, the PRAC concurred that no further regulatory action is needed at this point in time in light of current knowledge. Nevertheless, MAHs for amitriptyline-containing products should continue to monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for amitriptyline-containing products should continue to monitor the events of drug induced liver injury (DILI) and hepatocellular injury as part of routine safety surveillance.

4.3.2. Levonorgestrel[14] (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness

EPITT 18849 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAHs replied to the second request for information on the signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness and the responses were assessed by the Rapporteur.

Discussion

Having reviewed the available evidence, including the data provided by the MAHs and the data from studies performed by EMA, the PRAC agreed that the available evidence does not support an association between the use of levonorgestrel-releasing intrauterine device (IUD) with isolated anxiety disorder, panic disorder, sleep disorder or restlessness. Mood changes are considered included in the product information with the adverse drug reactions 'depressed mood' and 'depression'. Therefore, the PRAC concurred that no further regulatory action is needed at this point in time in light of current knowledge. Nevertheless, the MAHs for levonorgestrel-releasing intrauterine systems should continue to monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAHs for levonorgestrel-releasing IUD should continue to monitor the events of isolated anxiety disorder, panic attacks, mood changes, sleep disorders and restlessness as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

5.1.1. Andexanet alfa - EMEA/H/C/004108

Scope: Treatment of direct or indirect factor Xa (FXa) inhibitor when reversal of anticoagulation is needed

5.1.2. Binimetinib - EMEA/H/C/004052

Scope: Treatment of adult patients with unresectable or metastatic melanoma and treatment of unresectable melanoma with neuroblastoma RAS viral (V-ras) oncogene homolog (NRAS) Q61 mutation

[14] Intrauterine device (IUD)

5.1.3. Ertugliflozin - EMEA/H/C/004315

Scope: Treatment of type 2 diabetes mellitus (T2DM)

5.1.4. Ertugliflozin, metformin hydrochloride - EMEA/H/C/004314

Scope: Treatment of type 2 diabetes mellitus (T2DM)

5.1.5. Ertugliflozin, sitagliptin - EMEA/H/C/004313

Scope: Treatment of type 2 diabetes mellitus (T2DM)

5.1.6. Trastuzumab - EMEA/H/C/002575

Scope: Treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer (MGC)

5.1.7. Trastuzumab - EMEA/H/C/004361

Scope: Treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer (MGC)

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 15.2.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See also Annex I 15.3.

5.3.1. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0065

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of plaque psoriasis in adult patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 13) are updated accordingly

Background

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment, tumour necrosis factor alfa (TNFα) inhibitor indicated alone or in combination for the treatment of rheumatoid arthritis, for the treatment of axial spondyloarthritis including ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS, as well as for the treatment of psoriatic arthritis, under certain conditions.

The CHMP is evaluating an extension of the therapeutic indication for Cimzia, a centrally authorised product containing certolizumab pegol, to include treatment of plaque psoriasis in

adult patients. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Cimzia (certolizumab pegol) in the context of the extension of indication under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 13.0 and satisfactory responses to the request for supplementary of information (RSI) are submitted.
- Taking into account the available safety data for TNF inhibitor-containing medicines, including certolizumab pegol in approved indications, the experience in psoriasis with other TNF-inhibitors and the current product information for Cimzia (certolizumab pegol) that includes information relating to skin malignancies, which could be a particular concern in this new population, the PRAC concluded that there is no need for requesting an observational study in psoriasis patients at this point in time.

6. Periodic safety update reports (PSURs)

6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

See also Annex I 16.1.

6.1.1. Certolizumab pegol - CIMZIA (CAP) - PSUSA/00000624/201703

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment, tumour necrosis factor alfa (TNFα) inhibitor indicated alone or in combination for the treatment of rheumatoid arthritis, for the treatment of axial spondyloarthritis including ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS, as well as for the treatment of psoriatic arthritis, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cimzia, a centrally authorised medicine containing certolizumab pegol, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cimzia (certolizumab pegol) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to include 'worsening of symptoms of dermatomyositis' as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- The MAH should submit to EMA, within 6 months, a revised RMP including a discussion on the need for continuing with educational materials for prescribers.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.2. Empagliflozin - JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin, a biguanide. Empagliflozin, alone or in combination with metformin, is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Jardiance and Synjardy, centrally authorised medicines containing empagliflozin and empagliflozin/metformin respectively, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pyelonephritis and urosepsis as a warning and as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide further details on adverse drug reactions reported with empagliflozin in off-label use.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[15] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.3. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201703

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Yervoy (ipilimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on histiocytosis haematophagic in order to exercise caution when ipilimumab is given following or in combination with a programmed cell death protein 1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor. Histiocytosis haematophagic and pemphigoid should be also added as undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should closely monitor cases of rhabdomyolysis.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.4. Japanese encephalitis vaccine (inactivated, adsorbed) - IXIARO (CAP) - PSUSA/00001801/201703

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Japanese encephalitis vaccine (inactivated, adsorbed) is a vaccine indicated for active immunisation against Japanese encephalitis in adults, adolescents, children and infants aged 2 months and older.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ixiaro, a centrally authorised Japanese encephalitis vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

[17] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ixiaro (Japanese encephalitis vaccine (inactivated, adsorbed)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include syncope as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.5. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to *Corynebacterium diphtheriae* CRM_{197} protein) - MENVEO (CAP) - PSUSA/00001969/201703 (with RMP)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to *Corynebacterium diphtheriae* CRM_{197} protein) is a vaccine indicated for active immunisation of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W135 and Y, to prevent invasive disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Menveo, a centrally authorised meningococcal group A, C, W-135, Y conjugate vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Menveo (meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to *Corynebacterium diphtheriae* CRM_{197} protein)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a detailed review investigating the root cause of the observed peak in reconstitution errors reporting observed in the second half of 2016 within the EU, including proposals for appropriate measures as applicable as part of routine risk minimisation.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[18] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.6. Nintedanib[19] - OFEV (CAP) - PSUSA/00010319/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a tyrosine kinase inhibitor (TKI) indicated[20] in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ofev, a centrally authorised medicine containing nintedanib, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ofev (nintedanib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an analysis of cases of pulmonary embolism reported in the post-marketing setting and compare this population with the population included in INPULSIS-1[21] and INPULSIS-2[22] studies especially with regard to exclusion criteria. In addition, the MAH should ensure that cases with a plausible temporal relationship, cases reporting a positive dechallenge/rechallenge and cases reporting adequately managed underlying conditions are provided. Based on the presented data, the MAH should propose some wording to update the product information as appropriate.
- The MAH should submit to EMA, within 60 days, a detailed analysis of all available data relating to myocardial infarction, including a review of all post-marketing cases.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.7. Olaratumab - LARTRUVO (CAP) - PSUSA/00010541/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

[19] Respiratory indication only
[20] Nintedanib is also indicated in other indication(s) as part of separate marketing authorisation(s)
[21] A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral nintedanib 150 mg twice daily, on annual forced vital capacity decline, in patients with IPF (study 1199.32)
[22] A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral nintedanib 150 mg twice daily, on annual forced vital capacity decline, in patients with IPF (study 1199.34)

Olaratumab is a platelet derived growth factor receptor-α (PDGFR-α) antagonist indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lartruvo, a centrally authorised medicine containing olaratumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Lartruvo (olaratumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reactions/anaphylactic shock as part of the existing undesirable effect of infusion-related reactions. Therefore the current terms of the marketing authorisation(s) should be varied[23].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.8. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/201703 (with RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Raltegravir is an integrase strand transfer inhibitor active against the human immunodeficiency virus (HIV-1) indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Isentress, a centrally authorised medicine containing raltegravir, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Isentress (raltegravir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, a variation to reflect in the product information additional data and/or additional analysis to demonstrate the safe use in pregnancy of raltegravir and the lack of potential for foetotoxicity.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

[23] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.9. Zonisamide - ZONEGRAN (CAP) - PSUSA/00003152/201703

Applicant: Eisai Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Zonisamide is an antiepileptic benzisoxazole derivative indicated as monotherapy for the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy; and as adjunctive therapy for the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zonegran, a centrally authorised medicine containing zonisamide, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zonegran (zonisamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add information from a registry study on the risk of low birth weight and small for gestational age (SGA) in infants exposed to zonisamide *in utero* and to update information regarding the need to counsel women of child-bearing potential on the risk of anti-epileptic drugs (AEDs) in pregnancy. Therefore, the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a cumulative review of reports suggesting neuro-developmental defects in children exposed to zonisamide *in utero*. In addition, the MAH should provide a discussion of the analysis of cumulative reports of gingival hypertrophy, gingival pain and other terms which have been reported relating to disorders of the mouth. Finally, the MAH should provide any available updates relating to the data referred to in the study by *Hernandez-Diaz et al.*[25] or any information regarding low birth weight/small for gestational age (SGA) infants, requesting an update from the North American AED pregnancy registry if necessary.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[24] Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

[25] Association between topiramate and zonisamide use during pregnancy and low birth weight. Obstet Gynecol. 2014 Jan;123(1):21-8. DOI: 10.1097/AOG.0000000000000018

6.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See Annex I 16.2.

6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Fluticasone propionate (NAP) - PSUSA/00001454/201702

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Fluticasone propionate is a corticosteroid with anti-inflammatory activity. As inhaled formulations, fluticasone propionate is indicated for the prophylactic management of asthma. In some EU Member States, it is also indicated for the treatment of chronic obstructive pulmonary disease (COPD). As intranasal formulations, fluticasone propionate is indicated for the prophylaxis and treatment of seasonal allergic rhinitis including hay fever and perennial rhinitis. In some EU Member States, it is also indicated for nasal polyposis. As topical formulations, fluticasone propionate is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing fluticasone propionate, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fluticasone propionate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information for fluticasone propionate-intranasal formulations should be updated to include nasal ulcers as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[26].
- In the next PSUR, MAHs should review all information on growth reduction in children with a view to provide more detailed information in the product information regarding the size of the effect.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[26] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.2. Ibuprofen (NAP); ibuprofen lysine[27] (NAP) - PSUSA/00010345/201702

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Ibuprofen is a non-steroidal anti-inflammatory drug indicated[28] for the symptomatic relief of headache, toothache, sore throat, period pain, muscular and joint pain, back pain and minor arthritis pain. In addition, ibuprofen is indicated in the common cold or influenza for the symptomatic relief of pain and fever.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing ibuprofen, ibuprofen lysine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ibuprofen, ibuprofen lysine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated for medicinal products authorised for systemic use or products with substantial systemic release (oral, rectal, intravenous (IV), patch, and vaginal formulations) to include 'drug reaction with eosinophilia and systemic symptoms' (DRESS) as an undesirable effect with an unknown frequency. In addition, the product information should include a warning on metabolic acidosis in the context of overdose to inform of the symptoms and to advise patients to contact their physician. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, MAHs should provide a safety review regarding the potential association between ibuprofen and photosensitivity and discuss the need to update the product information if necessary. In addition, all MAHs of medicinal products authorised for systemic use or substantial systemic release (oral, rectal, IV, patch, and vaginal) should provide a review regarding the potential association between ibuprofen and pancreatitis. MAHs should also provide a review on off-label use of ibuprofen in closure of the patent ductus arteriosus (PDA) in order to assess the risks associated with PDA treatment. Finally, all MAHs of oral formulations of ibuprofen- and ibuprofen lysine-containing medicines[30] should provide a detailed review regarding intestinal diaphragm-like strictures.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[27] All indications except ductus arteriosus
[28] All indications except ductus arteriosus
[29] Update of SmPC sections 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[30] Not indicated in ductus arteriosus

6.3.3. Lanthanum (NAP) - PSUSA/00003175/201703

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Lanthanum is a phosphate binding agent indicated for the treatment of hyperphosphatemia in chronic renal failure patients on dialysis and in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥ 1.78 mmol/L (≥ 5.5 mg/dL) in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

The PRAC is currently reviewing the benefit-risk balance of nationally authorised medicines containing lanthanum, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the December 2017 PRAC meeting.

Summary of conclusions

The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting. To this effect, the PRAC requested supplementary information from the MAH. Further discussion and adoption of a recommendation is planned at the December 2017 PRAC meeting.

6.3.4. Mefloquine (NAP) - PSUSA/00001955/201702

Applicant(s): various

PRAC Lead: Kristin Thorseng Kvande

Scope: Evaluation of a PSUSA procedure

Background

Mefloquine is an antimalarial indicated for the treatment and prophylaxis of malaria.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing mefloquine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mefloquine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include insomnia as a warning and as an undesirable effect with a very common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[31].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[31] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.5. Promestriene[32] (NAP) - PSUSA/00009271/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Promestriene is a synthetic oestrogen indicated as capsules for the treatment of vaginal atrophy by oestrogen deficiency and as cream for the treatment of vulvar, vestibular and vaginal atrophy.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing promestriene, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of promestriene-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'vaginal bleeding' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[33].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.6. Sodium iodide (^{131}I) (NAP) - PSUSA/00002753/201703

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Sodium iodide (^{131}I) is a radiopharmaceutical indicated as a diagnostic agent for the evaluation of thyroid function, determination of the functionality of thyroid nodules, and evaluation of the thyroid tissue and metastasis in thyroid cancers. In addition, it is indicated as a therapeutic agent for the treatment of hyperthyroidism and of differentiated thyroid tumour.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing sodium iodide (^{131}I), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

[32] Cream and vaginal capsules only
[33] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of sodium iodide (^{131}I)-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of sodium iodide (^{131}I)-containing products indicated in therapy should be updated to include a warning on hyponatraemia to alert healthcare professionals to consider undertaking regular serum electrolyte measurements in patients at risk. Therefore the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAHs should present a cumulative review of cases of sialoadenitis and discuss possible risk minimisation measures. The MAHs should also discuss the need to update the product information as necessary.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Rituximab – MABTHERA (CAP) – EMEA/H/C/000165/LEG 0096

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Cumulative review of T lymphocyte decrease overall, CD4+ and CD8+ lymphocyte decrease using all relevant data sources (spontaneous reports, clinical trials, literature) split by indication, focussing on data sources in which rituximab was used as monotherapy. In addition, cumulative review on the incidence of progressive multifocal leukoencephalopathy (PML) in rituximab treated patients stratified by indication and clinical setting using all available information, including an in-depth review of all risk factors for PML in rituximab treated patients, a discussion on the need for PML risk stratification strategies and proposals for a risk stratification algorithm and risk minimisation measures depending on the risk level, as requested in the conclusions of PSUSA/00002652/201611 adopted in June 2017

Background

Rituximab is a monoclonal antibody that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes and is indicated in adult patients for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and rheumatoid arthritis (RA) as well as for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) under certain conditions.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes June 2017). While the responses are being assessed by the Rapporteur for further

[34] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC advice due at the December 2017 PRAC meeting[35], PRAC considered a cross-sectional study on the data on EudraVigilance, with the aim to characterise the reported risk factors described in the reports of cases of progressive multifocal leukoencephalopathy (PML), in particular the CD4 lymphocyte count. In addition, the Committee further discussed on the consultation of the inter-committee Scientific Advisory Group on oncology (IC-SAG-O).

Summary of advice/conclusion(s)

The PRAC discussed the preliminary assessment prepared by the Rapporteur together with the cross-sectional study on the data on EudraVigilance. The Committee also adopted a list of questions for the IC-SAG-O organised on 22 November 2017.

Post-meeting note: on 22 November 2017, the Committee adopted by written procedure a list of experts (LoE) for the IC-SAG-O meeting.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[36]

See also Annex I 17.1.

7.1.1. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/PSA/S/0023

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Doris Stenver

Scope: Amendment to a previously agreed protocol for a prospective, multicentre registry (TED-R-13-002) for patients with short bowel syndrome in order to evaluate the long-term safety profile for patients with short bowel syndrome (SBS) who are treated with teduglutide in a routine clinical setting [protocol previously adopted within procedure EMEA/H/C/002345/ANX 003.7 at the May 2014 PRAC meeting]

Background

Revestive is a centrally authorised medicine containing teduglutide, a glucagon-like peptide-2 (GLP-2) analogue. It is indicated for the treatment of patients aged 1 year and above with short bowel syndrome (SBS).

In July 2013 and May 2014, the PRAC adopted a protocol for a non-interventional PASS (TED-R13-002) designed to evaluate the long-term safety profile for patients with short bowel syndrome (SBS) who are treated with teduglutide in a routine clinical setting. For further background, see PRAC minutes July 2013 and PRAC minutes May 2014.

Further to the MAH's submission of a substantial protocol amendment to add new items to the data to be collected during the study (e.g. for paediatric patients, their significant medical history, enteral nutrition history and enteral nutrition adjustments, as well as for adult and paediatric patients their urine output measures), to expand effectiveness analyses to include further stratifications and to add the definitions of adverse events (AE) of special

[35] Scheduled on 27-30 November 2017
[36] In accordance with Article 107n of Directive 2001/83/EC

interest as per the identified risks of the product, the amended protocol (version 4.1) was reviewed by the PRAC.

Endorsement/Refusal of the protocol

- The PRAC, having considered the revised protocol version 4.1 in accordance with Article 107n of Directive 2001/83/EC, considered that the study is non-interventional and the substantial amendments to the PASS protocol (TED-R13-002) for teduglutide (Revestive) can be endorsed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[37]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[38]

7.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0010

Applicant(s): Janssen (on behalf of a consortium)

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS imposed as an outcome of the Article 31 referral (EMEA/H/A-31/1365) in September 2014, to assess the effectiveness of the risk minimisation measures of domperidone – a physician survey

Background

Domperidone is a D_2-receptor antagonist indicated for the relief of the symptoms of nausea and vomiting. In line with the conclusions dated 2014 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1365) conducted by the PRAC for domperidone-containing medicines, MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study in several Member States to assess the effectiveness of the agreed risk minimisation measures and to monitor off-label use. The study protocol was to be submitted within 3 months after the European Commission decision. In January 2016, the PRAC endorsed the PASS (drug utilisation study (DUS)) protocol version 3 (dated 12 October 2015) submitted by the MAH Janssen Research and Development on behalf a group of MAHs (the Domperidone Collaboration Study Group). For further background, see PRAC minutes March 2014, PRAC minutes April 2015, PRAC minutes September 2015 and PRAC minutes January 2016.

The final study report was submitted to EMA by the MAH Janssen Research and Development on behalf a group of MAHs (Domperidone Collaboration Study Group) on 29 August 2017. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled `a post-authorisation safety study (PASS) to assess the effectiveness of the risk minimisation

[37] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[38] In accordance with Article 107p-q of Directive 2001/83/EC

measures of domperidone – physician survey', the PRAC considered that supplementary information was required before a recommendation could be made on the benefit-risk balance of medicinal products containing domperidone concerned by the PASS final report.

- The MAHs should perform multivariate analyses to better characterise prescribers' profile with incorrect answers.
- The MAH should submit responses to the request for supplementary information within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.3.2. Flupirtine maleate (NAP) - EMEA/H/N/PSR/J/0007

Applicant(s): Meda Pharma GmbH & Co KG, DE and Meda Pharma - Produtos Farmaceuticos, S.A. PT (Flupigil, Metanor); various (on behalf of a consortium)

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to EMEA/H/N/PSR/J/0007 [final study results for an imposed non-interventional PASS EUPAS11134: a retrospective chart review to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice] as per the request for supplementary information (RSI) adopted by PRAC in July 2017

Background

Flupirtine is a pyridine derivative used as an analgesic for acute pain, in moderate-to-severe cases.

The PRAC discussed the final study results and the responses to the requests for supplementary information submitted by the MAH. For further background, see PRAC minutes March 2017 and PRAC minutes July 2017.

Summary of recommendation(s) and conclusions

- Based on the PRAC review of the PASS final study report, the PRAC considered that a wider EU review including all flupirtine-containing products is warranted to enable the assessment of all the available data related to the risk of hepatic injury and its impact on the benefit-risk of these products.

See also under 3.1.1.

7.3.3. Hydroxyethyl starch (NAP) - EMEA/H/N/PSR/S/0009

Applicant(s): Fresenius Kabi Deutschland GmbH (Volulyte, Voluven; various)

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to EMEA/H/N/PSR/S/0009 [results of a retrospective drug utilisation study (DUS) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions in hospital settings] as per the request for supplementary information (RSI) adopted by PRAC at its October 2017 meeting

Background

Hydroxyethyl starch (HES) products derive from potato or corn with different molecular weights and substitution ratios (e.g. 200/0.5; 130/0.4).

The final study report was submitted to EMA by MAH Fresenius Kabi Deutschland GmbH on 5 July 2017. The PRAC discussed the final study results and the responses to the request for supplementary information submitted by the MAH. For background, see PRAC minutes October 2017.

Summary of recommendation(s) and conclusions

- Based on the PRAC review of the PASS final study report version 1.0, the PRAC considered that a wider EU review including all HES-containing products is warranted to assess the newly available data related to HES-containing products and their impact on the benefit-risk balance of these products.

See also under 2.1.1.

7.3.4. Thiocolchicoside (NAP) - EMEA/H/N/PSR/J/0008

Applicant(s): Sanofi (on behalf of a consortium)

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of the effectiveness of risk minimisation measures: a joint PASS survey among healthcare professionals (HCPs) to assess their knowledge and attitudes on prescribing conditions of thiocolchicoside containing medicinal products for systemic use in France, Greece, Italy and Portugal

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. In line with the conclusions dated 2013 of the referral procedure , under Article 31 of Directive 2001/83/EC (EMEA/H/A-1361) conducted by the CHMP for thiocolchicoside-containing medicines, the MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study (DUS) in several Member States to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription. The European Commission decision was issued on 17 January 2014. The MAHs submitted a joint DUS protocol version 1.0 on 17 July 2015. In September 2016, the PRAC endorsed the PASS (DUS and survey) protocol version 3.0 dated 26 April 2016 submitted by the MAH Sanofi-Aventis Recherche & Développement on behalf a group of MAHs (including Sanofi Aventis Groupe and 25 other companies involved in the consortium). For further background, see PRAC minutes September 2015, PRAC minutes October 2015, PRAC minutes March 2016, and PRAC minutes September 2016.

The final study report of the joint PASS survey was submitted to EMA by the MAH Sanofi-Aventis Recherche & Developpement/Sanofi Aventis groupe and other companies involved in the consortium on 14 August 2017. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'evaluation of the effectiveness of risk minimisation measures: a joint PASS survey among healthcare professionals (HCPs) to assess their knowledge and attitudes on prescribing conditions of thiocolchicoside-containing medicinal products for systemic use

in France, Greece, Italy and Portugal', the PRAC considered that supplementary information was required before a recommendation could be made on the benefit-risk balance of medicinal products containing-thiocolchicoside concerned by the PASS final report.

- The consortium of MAHs should comment on the high proportion of HCPs that stated that they did not receive the educational materials as well as explaining the possible reasons for differences between the receipt of a direct healthcare professional communication (DHPC) versus educational materials, differences between the countries and HCPs. In addition, the MAHs should discuss the need for additional risk minimisation measures besides those implemented following the referral procedure completed in 2014 in the view of the preliminary conclusions of the survey as well as in the view of the additionally requested information part of the request for supplementary information (RSI).
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 days-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[39]

See Annex I 17.4.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

[39] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the agenda.

9.3. Others

None

10. Other safety issues for discussion requested by the CHMP or the EMA

10.1. Safety related variations of the marketing authorisation

None

10.2. Timing and message content in relation to Member States' safety announcements

None

10.3. Other requests

None

10.4. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

11. Other safety issues for discussion requested by the Member States

11.1. Safety related variations of the marketing authorisation

11.1.1. Leuprorelin acetate (NAP)

Applicant: Astellas Pharma (Eligard, Eliprogel)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the distribution of a direct healthcare professional communication (DHPC) in the context of safety related type II variations (Eligard: DE/H/0580/001-003/II/072; Eliprogel: DE/H/4014/001-003/II/014) to update the product information with additional reconstitution guidance related to safety needle

Background

Leuprorelin is a gonadotropin-releasing hormone (GnRH) agonist binding to the GnRH receptors used in various indications including the treatment of prostate cancer.

After the implementation of a new safety needle for Eligard (leuprorelin acetate) in 2013, an increased number of cases of handling errors regarding needle leakage due to overtightening of the safety needle hub have been reported. In the context of the evaluation of a type II variation procedure including a direct healthcare professional communication (DHPC) on the needle issues due to overtightening to be distributed in all Member States, Germany requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the need for a DHPC concerning the product information update with additional reconstitution guidance related to the safety needle for Eligard/Eliprogel (leuprorelin). The PRAC advised that changes should be made to the wording of the DHPC in line with comments from Member States. In addition, the PRAC supported the proposed communication plan and advised that the dissemination of the communication should be agreed on a national level in the Member States where the product is marketed.
- The PRAC also supported the amendment of the approved educational materials (poster, smartphone application, website and video), and the submission of a variation to update the RMP following the approval of variations DE/H/0580/001-003/II/072 and DE/H/4014/001-003/II/014 for Eligard and Eliprogel respectively.

11.1.2. Misoprostol[40] (NAP)

Applicant: Ferring Läkemedel AB (Misodel)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a safety related variation (MRP SE/H/1224/01/II/04/G) updating of the product information[41] and including a direct healthcare professional communication (DHPC) to ensure the correct use of the medicinal product

Background

Misoprostol is a synthetic prostaglandin E1 analogue indicated for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated as well as for expansion of the non-pregnant uterine cervix before hysteroscopy or other gynaecological procedures requiring access to the uterine cavity.

Following the assessment of the latest PSUSA, PSUSA/00010353/201605 (see PRAC minutes January 2017), the MAH was requested to submit two type II variations in order to revise the frequency of some undesirable effects in the product information, and to suggest improvements to ensure correct use of the medicinal product. Moreover, the MAH was asked to consider the need for additional communication activities, such as a direct healthcare professional communication (DHPC). The MAH submitted a group of variations taking all aspects into account. In the context of the evaluation of the above mentioned grouped type II variation procedure, Sweden requested PRAC advice on its assessment regarding the product information updates and the content of a proposed DHPC and communication plan.

Summary of advice

- Based on the available data, the PRAC discussed the Member State's request for PRAC advice on Misodel 200µg (vaginal insert) and the safety related variation to revise the adverse drug reaction (ADR) frequencies in the product information based on crude incidence during clinical trials.
- Overall, the PRAC endorsed the assessment conducted by Sweden, the reference member state (RMS), of the safety related variation. In particular, the PRAC supported the proposed revisions of the product information[42] regarding the timing to remove the vaginal insert and the warning regarding the risk of excessive uterine tachysystole.
- In addition, the PRAC agreed on the content of a DHPC and communication plan and supported its distribution at the EU national level where the product is marketed.

11.2. Other requests

11.2.1. Ethylmorphine (NAP); tramadol (NAP)

Applicant(s): various

PRAC Lead: Julie Williams

Scope: PRAC consultation on the scientific relevance to update the product information of

[40] Vaginal insert formulation, containing 200 µg of misoprostol
[41] Proposal to update SmPC sections 4.2, 4.4, 4.8, 5.1 and the package leaflet
[42] Proposal to update SmPC sections 4.2 and 4.4

tramadol-containing products and ethylmorphine-containing products regarding the use in the paediatric population given the metabolism of tramadol and ethylmorphine, available safety data, and the changes made in the context of the codeine referral for pain (EMEA/H/A-31/1342) concluded in 2013 as well as in the codeine referral for cough and/or cold (EMEA/H/A-31/1394) concluded in 2015

Background

Ethylmorphine, oxycodone and tramadol are opioid/semi-synthetic opioid analgesics which are metabolised via CYP2D6[43]. Codeine has been previously discussed in 2013 in the context of a safety signal which triggered a referral procedure under Article 31 of Directive 2001/83/EC leading to restrictions of use of codeine for pain in children (EMEA/H/A-31/1342). A further referral under Article 31 of Directive 2001/83/EC led in 2015, where appropriate, to similar restrictions with regard to the use of codeine in cough and/or colds in children (EMEA/H/A-31/1394). The CHMP Pharmacogenomics Working Party (PgWP) also provided its views on the differences of the metabolism between codeine and dihydrocodeine, and the clinical implications of the CYP2D6 genetic polymorphisms.

The CMDh was requested by a Member State to consider whether the extent of the recommendations agreed for codeine would apply to other codeine derivatives. This followed action taken by the Belgian Medicines Agency (FAMHP) with regard to ethylmorphine-containing products to introduce restrictions similar to those that were introduced for codeine-containing products used for cough and cold as a result of the outcome of the referral procedure EMEA/H/A-31/1394. In order to support further discussion on this point, the PgWP was further requested to provide its views on the differences of the metabolism between codeine and other codeine derivatives, and whether clinical implications of CYP2D6 genetic polymorphisms on formation of morphine may be extrapolated to these derivatives as well. The PgWP considered that there should be further evaluation of the need for modification of the product information for tramadol- and ethylmorphine-containing products to include a general warning concerning CYP2D6 metabolism

Consequently, PRAC advice was sought on the scientific relevance to update the product information of tramadol-containing products and ethylmorphine-containing products regarding use in the paediatric population given the metabolism of tramadol and ethylmorphine, and the available safety data, as well as the changes made in the context of the codeine referral for pain (EMEA/H/A-31/1342) and the codeine referral for cough and/or cold (EMEA/H/A-31/1394).

Summary of advice

- The PRAC considered the evaluation conducted to date and noted that this had taken into account information available on metabolism including relevant published literature, as well as the conclusions of the PgWP and available safety data.
- Whilst the PRAC supported the need to introduce warnings in line with those introduced following the codeine referral procedures, given the limitations of the data and questions that had been raised as to whether the clinical implications of CYP2D6 polymorphisms for ethylmoprhine and tramadol were the same as those for codeine, it was considered important to obtain further information before deciding on more restrictive measures, such as the introduction of contraindications. It was also considered necessary to fully understand the clinical utility of these products in the paediatric populations in member

[43] Cytochrome P450 2D6

states and, in this respect, it was agreed that it would be valuable to seek the views of the PDCO as well as obtaining further information on the recent trends in exposure data in the paediatric population and clinical use of these substances in the paediatric population, especially as this may differ across Member States. Consequently, the PRAC adopted a list of questions (LoQ) to consult the PDCO.

- The PRAC noted that a PSUSA procedure for tramadol (PSUSA/00003002/201705) is scheduled for PRAC recommendation at the January 2018 meeting and considered that this would provide the opportunity to further consider this issue alongside the additional data and views of the PDCO.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Brexit ancillary working group

PRAC lead: Almath Spooner

At the organisational matters teleconference held on 9 November 2017, the chair of the PRAC ancillary working group on Brexit preparedness updated the PRAC.

See also under 12.4.1.

12.2. Coordination with EMA Scientific Committees or CMDh

12.2.1. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP)

PRAC lead: Brigitte Keller-Stanislawski, Dolores Montero Corominas, Sabine Straus, Ulla Wändel Liminga, Julie Williams

Following the previous PRAC discussion on the draft revised Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' (see PRAC minutes October 2017), PRAC adopted the document for further endorsement at CAT and CHMP prior to its release for a three month-public consultation period.

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

12.3.1. Scientific advice working party (SAWP) – re-nomination of PRAC representative(s)

In December 2016, the CHMP Scientific Advice Working Party (SAWP) adopted a revised mandate with a new composition including a chairperson, a vice-chair, 24 members, each with an alternate as well as 1 to 3 joint members from COMP, CAT, PDCO and PRAC. The mandate foresees re-nomination of all SAWP members every three years to enable the working party to take advantage of the best and most relevant expertise from across the

network. It also foresees that one year after the chairperson's election the CHMP shall re-examine and confirm the composition of the entire SAWP. Therefore, the EMA Secretariat invited PRAC delegates to express interest in fulfilling the role of joint PRAC-SAWP members by 21 November 2017. The PRAC will endorse the nominations at the December 2017 PRAC meeting[44] for further discussion at the SAWP and final endorsement of the SAWP's composition at the December 2017 CHMP meeting.

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit: preparedness of the regulatory network and capacity increase

The EMA Secretariat provided PRAC with a status update on the Brexit preparedness activities, including an update on the next steps.

See also under 12.1.1.

12.5. Cooperation with International Regulators

None

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

12.7.1. PRAC work plan 2018 – preparation

PRAC lead: June Raine, Almath Spooner

At the organisational matters teleconference held on 9 November 2017, the EMA Secretariat presented to PRAC a draft PRAC work plan for 2018. Further discussion will take place in January 2018.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions

The EMA secretariat presented, at the organisational matters teleconference held on 9 November 2017, quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, where available, and per EU National Competent Authority (NCA) for the upcoming months. For previous update, see PRAC minutes July 2017.

[44] On 27-30 November 2017

12.8.2. PRAC workload statistics – Q3 2017

The EMA secretariat presented, at the organisational matters teleconference held on 9 November 2017, quarterly figures to provide metrics on the evolution of the workload of the PRAC, by reflecting the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see PRAC minutes July 2017.

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections - Union procedure on follow-up of pharmacovigilance inspections

Following up from the previous PRAC discussion on the draft template for sharing information 'from assessors to inspectors' (see PRAC minutes October 2017), the EMA Secretariat also presented to PRAC at the current meeting the draft 'Union procedure on the follow-up of pharmacovigilance inspections', applying to both CAPs and NAPs, defining the steps in the follow-up of pharmacovigilance inspections and the responsibilities of the parties involved. This includes the process for requesting a corrective and preventive action (CAPA) plan in writing from the MAH, CAPA plan review and approval by the inspectors, routine interaction within and between EU Member States and the EMA as well as actions to be taken following the identification of inspection findings which may impact on the robustness of the benefit-risk profile of medicinal product(s), and re-inspection planning. As post-inspection actions may also involve assessors in the EU Member States, EMA and Committees, PRAC delegates were invited to provide written comments by 17 November 2017.

12.9.3. Pharmacovigilance audits

None

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the progress made.

12.10.3. PSURs repository

None

12.10.4. PSUR roadmap - explanatory note to Good Pharmacovigilance Practice (GVP) module VII on 'Periodic safety update report' and 'Questions & Answers (Q&A)' document to assessors - update

PRAC lead: Menno van Der Elst, Ulla Wändel Liminga

Following the joint industry/assessor webinar training held at EMA on 22 September 2017 (for further background, see PRAC minutes October 2017), the EMA Secretariat presented to PRAC an update to the explanatory note to GVP module VII on 'Periodic safety update report' (PSUR) (EMA/102307/2017) and an update to the 'Q&A for assessors on PSUSA: guidance document for assessors' (EMA/518909/2016). Both documents have been updated in relation to the definitions of the safety concerns in the RMP and in the PSUR brought about by the introduction of revision 2 of GVP module V on 'risk management systems' as well as MAHs' new requirements for EudraVigilance monitoring. In addition, the explanatory note has been updated to include the requirement to submit PSURs in English and the Q&A for assessors has been updated to reflect that follow-up to PSUSA procedures should be avoided when the PSUR frequency for an active substance or a combination of active substances is yearly or less. PRAC delegates were invited to provide written comments by 30 October 2017.

Post-meeting note: On 31 October 2017, the PRAC adopted the updated explanatory note to GVP module VII and the updated Q&A for assessors on PSUSA by written procedure. Following adoption at the November 2017 CMDh, the updated explanatory note to GVP VII and Q&A on PSUSA were published on 13/11/2017 on the EMA website.

12.10.5. Union reference date list – consultation on the draft list

The PRAC endorsed the draft revised EURD list version November 2017 reflecting the PRAC's comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of November 2017, the updated EURD list was adopted by the CHMP and CMDh at their November 2017 meetings and published on the EMA website on 15/11/2017, see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)

12.11. Signal management

12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) work stream WS1 meeting held on 23 October 2017. The SMART WG WS1 initiated a discussion on the signal procedure process, in particular the nature and timing of documents shared with MAHs. The WG also discussed the draft work plans 2018 for the two work streams rebranded as 'Processes (ex-WS1)' and 'Methods (ex-WS 2-3)' to reflect their immediate scopes. Further discussion will take place at the December 2017 WG WS1 meeting. Finally, as a follow-up to discussions dated 2016 on emerging safety issues (ESI) and NCA contact points, the WG was informed that the EMA website includes now a section on 'how to report issues with an authorised product' under emerging safety issues (ESI).

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 29/11/2017 on the EMA website

(see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project – update and next steps

Following previous discussions (see PRAC minutes June 2017, PRAC minutes July 2017 and PRAC minutes September 2017), the EMA Secretariat further updated the PRAC on the EudraVigilance auditable requirement project in view of the planned go-live of the new EudraVigilance system on 22 November 2017. Details on stakeholder support and training were also presented. Further updates and information are scheduled at the December 2017 PRAC meeting[45].

[45] Scheduled on 27-30 November 2017

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation safety studies (PASS)

None

12.15.1. Post-authorisation Safety Studies – non-imposed PASS

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Strategy on measuring the impact of pharmacovigilance – revised activities

PRAC lead: Marieke de Bruin

At the organisational matters teleconference held on 9 November 2017, the EMA Secretariat presented, on behalf of the PRAC Interest Group (IG) impact, a draft revision to the 'PRAC impact strategy for measuring impact of pharmacovigilance activities' (EMA/790863/2015) in line with the PRAC IG impact work plan 2017. A draft work plan for 2018 was also presented. PRAC members were invited to send comments by 23 November 2017. Further discussion will take place at the December 2017 PRAC meeting[46] with a view to adoption of the revised PRAC impact strategy document, including the work plan for 2018.

12.20.2. Serious cutaneous adverse reactions (SCARs) - regulatory perspective

PRAC lead: Sabine Straus, Herve Le Louet, Zane Neikena

As a follow-up to the last discussions on the draft guidance document on serious cutaneous adverse reactions (SCARs) (see PRAC minutes April 2017), the PRAC leads and EMA Secretariat presented to PRAC the consolidated guidance for endorsement, aiming at supporting assessors to review data presented on SCARs in individual case safety reports (ICSR), assess causality and decide on the appropriate regulatory reflection of SCARs in product information in both SmPC and PIL as well as in RMPs. The PRAC adopted the guidance on SCARs as a working document. The document will be revisited in 2018 after a period of piloting to include experience gained and comments gathered over time.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[47]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[48].

[46] on 27-30 November 2017
[47] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required
[48] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.1. Efavirenz – SUSTIVA (CAP), STOCRIN (CAP); tenofovir disoproxil - VIREAD (CAP); emtricitabine – EMTRIVA (CAP); efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG (Sustiva), Merck Sharp & Dohme Limited (Stocrin), Gilead Sciences International Limited (Viread, Emtriva, Atripla)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

EPITT 18956 – New signal

Lead Member State(s): PT, FR, UK, DE

14.1.2. Eltrombopag – REVOLADE (CAP)

Applicant(s): Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Signal of laboratory test interference, interference with bilirubin assay

EPITT 18955 – New signal

Lead Member State: ES

14.1.3. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of oesophagitis

EPITT 18954 – New signal

Lead Member State: SE

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

None

15.2. Medicines in the post-authorisation phase – PRAC-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

15.2.1. Aclidinium, formoterol - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1221/0017; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1221/0017

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 3) to re-categorise 'hypersensitivity (anaphylactic responses, angioedema, and urticaria)' from important potential risk to important identified risk, remove 'use in non-Caucasian patients' as missing information (with the completion of clinical studies in Asian patients), and include milestones and due dates for PASS D6560R00004: an aclidinium bromide PASS to evaluate the risk of cardiovascular endpoints and a drug utilisation study (DUS) (D6560R00002): common for aclidinium (DUS1) and aclidinium/formoterol fixed-dose combination (DUS2) to describe the characteristics and patterns of use of new users of aclidinium bromide (monotherapy or in combination) and new users of other medications for chronic obstructive pulmonary disease (COPD), to evaluate the potential for off-label use and to describe users of aclidinium (monotherapy or in combination) in patient subgroups for which there is missing information

15.2.2. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/II/0029/G

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variations to: 1) update the RMP to amend the category 3 study 201805: an observational study of the risk of common malignant neoplasms and malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to those prescribed other antidiabetic agents, in order to use a different database to study the risk of neoplasms in association with albiglutide exposure; 2) update the RMP to add a new category 3 study as an additional pharmacovigilance activity study 207351: an observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy

15.2.3. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0027, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Updated RMP (version 4.0) in order to re-classify an imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) aiming at recording safety and outcome data in patients diagnosed with severe veno-occlusive disease (VOD) following haematopoietic stem cell transplantation (HSCT) treated or not with Defitelio. Annex II of the product information is updated accordingly

15.2.4. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/II/0024, Orphan

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: Updated RMP (version 3.1) in order to submit protocol amendments of SHP617-400 (EU-AIR) study: a European multicentre, multi-country, post-authorisation, observation study (registry) of patients with chronic adrenal insufficiency (category 3). In addition, the MAH took the opportunity to implement a change agreed by the PRAC/CHMP as part of the assessment of MEA 005.3 dated July 2016 to remove from the RMP reference to study SHP617-404 (SWE-DUS): a category 3 study to monitor off-label use of Plenadren to evaluate physician prescribing patterns

15.2.5. Insulin human - ACTRAPHANE (CAP) - EMEA/H/C/000427/WS1197/0072; ACTRAPID (CAP) - EMEA/H/C/000424/WS1197/0066; INSULATARD (CAP) - EMEA/H/C/000441/WS1197/0069; MIXTARD (CAP) - EMEA/H/C/000428/WS1197/0073; PROTAPHANE (CAP) - EMEA/H/C/000442/WS1197/0068

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Updated RMP (version 2.1) in line with the Guidance on format of the RMP in the EU (revision 2). Moreover, significant changes to the safety specification are proposed with this RMP update as some risks are now considered fully characterised and appropriately managed: 1) removal of the following important identified risks: hypoglycaemia, anaphylactic reactions, peripheral neuropathy, refraction disorders, lipodystrophy, urticaria, rash, oedema and diabetic retinopathy; 2) removal of the following important potential risks: immunogenicity, allergic reactions and lack of efficacy related to the new manufacturing process; and 3) removal of the following missing information: special patient groups

15.3. Medicines in the post-authorisation phase – CHMP-led procedure

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0056

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include a new indication for Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe for the treatment of active Still's disease, including systemic juvenile idiopathic arthritis and adult-onset Still's disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and package leaflet

15.3.2. Atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/WS1193/0018; REYATAZ (CAP) - EMEA/H/C/000494/WS1193/0113

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Caroline Laborde

Scope: Update of sections 4.3 and 4.5 of the SmPC to include information on the contraindicated co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination used for the treatment of chronic hepatitis C infection following the results of interaction studies. The Package Leaflets and the RMPs (Evotaz (version 5.0), Reyataz (version 13.0)) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes and typographical corrections in the Reyataz and Evotaz Product Information

15.3.3. Avanafil - SPEDRA (CAP) - EMEA/H/C/002581/II/0027/G

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variation consisting of: 1) update of section 4.4 to reflect the results of clinical study TA-402: a double-blind, randomized, placebo-controlled, single-dose, parallel study to assess the effects of avanafil on multiple parameters of vision, including, but not limited to visual acuity, intraocular pressure, pupillometry, and colour vision discrimination, in healthy male subjects; 2) update of section 4.6 of the SmPC in order to reflect the results of clinical study TA-401: a randomized, double-blind, placebo-controlled, parallel group, multicentre clinical trial of the effect of avanafil on spermatogenesis in healthy adult males and adult males with mild erectile dysfunction. The Package Leaflet and the RMP (version 5.1) are updated accordingly. In addition, the MAH took the opportunity to make an editorial correction on the approved SmPC by adding the missing adverse reaction epistaxis from the tabulated list of adverse reactions reported in section 4.8. Additionally, the MAH took the opportunity to align the information of Package Leaflet section 3 to SmPC section 4.2

15.3.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of sections 4.5 and 5.2 of the SmPC, based on the final study report of an in vitro study investigating the inhibitory effect of baricitinib on the organic anion transporter 2 (OAT2) in fulfilment of MEA 001. The RMP (version 3.0) is updated accordingly

15.3.5. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0025/G, Orphan

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukaemia

(CML) for Bosulif based on study AV001: a multicentre phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed CP CML. In addition, the MAH updated the SmPC with safety and efficacy data from study B1871006: a phase 1/2 study of bosutinib in Ph+ leukaemias, and study B1871008: a phase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed CP Ph+ CML. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly. Furthermore, Annex IIIA is brought in line with the latest QRD template (version 10)

15.3.6. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0048, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients with $CD30^+$ cutaneous T-cell lymphoma (CTCL) who require systemic therapy, based on data from study C25001 ('ALCANZA' study): a phase 3 trial of brentuximab vedotin (SGN-35) versus physician's choice (methotrexate or bexarotene) in patients with cd30-positive cutaneous t-cell lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 10) are updated accordingly

15.3.7. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0002/G

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Update of section 5.1 of the SmPC to reflect the final study results from clinical study XL184-308: a phase 3, randomized, controlled study of cabozantinib (XL184) *vs* everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitor therapy, to fulfil the condition to the marketing authorisation listed as a post-authorisation efficacy study (PAES) in Annex II. The RMP (version 2.0) is updated accordingly

15.3.8. Certolizumab pegol - CIMZIA (CAP) - EMEA/H/C/001037/II/0060

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update the information on pregnancy and lactation based on two pharmacokinetic (PK) studies evaluating the transfer of Cimzia into breastmilk (UP0016 study: a multicentre, post-marketing study to evaluate the concentration of certolizumab pegol in the breast milk of mothers receiving treatment with Cimzia phase 1B (clinical pharmacology) study) and via the placenta (UP0017 study: a multicentre post-marketing study to evaluate the placental transfer of certolizumab pegol in pregnant women receiving treatment with Cimzia). The Package Leaflet and the RMP (version 12) are updated accordingly

15.3.9. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0068

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture as well as the prevention of osteoporosis in women and men at increased risk of fracture who are starting or have recently started long-term glucocorticoid therapy. As a consequence, sections 4.1 and 5.1 of the SmPC are updated to reflect the new indications based on the analysis of the data from the pivotal study glucocorticoid-induced osteoporosis (GIOP): study 20101217: a randomized, double-blind, active controlled study evaluating the efficacy and safety of denosumab compared with risedronate in glucocorticoid-treated individuals. The Package Leaflet and the RMP (version 19.0) are updated accordingly

15.3.10. Denosumab - XGEVA (CAP) - EMEA/H/C/002173/II/0055

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours for Xgeva. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 24.0) are updated accordingly

15.3.11. Idarucizumab - PRAXBIND (CAP) - EMEA/H/C/003986/II/0007

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the final results from study 1321.3, the RE-VERSE-AD study (reversal effects of idarucizumab on active dabigatran): a phase 3 case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures - RMP category 3 study (MEA 001). The RMP (version 3.0) is updated accordingly. In addition, the MAH took the opportunity to update the immunogenicity section in 5.1 of SmPC and to bring the product information (PI) in line with the latest QRD template (version 10)

15.3.12. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/II/0032/G

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of: 1) extension of indication of the approved chronic lymphocytic leukaemia (CLL) indication for Zydelig to include its use in combination with bendamustine and rituximab based on the results of the primary analysis of pivotal study

GS-US-312-0115: a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 2.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet; 2) submission of the final clinical study report (CSR) for study 101-08: a phase 2, single-arm study which evaluated idelalisib as monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma. Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL, and fulfilment of PAM008; 3) submission of the final clinical study report (CSR) for study GS-US-312-0123: a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL

15.3.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0204

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final registry report from C0168T71 study: a review and analysis of birth outcomes from Swedish, Danish and Finish medical birth registers and an evaluation of pregnancy data from multiple sources. Section 4.6 of the SmPC, the Package Leaflet and the RMP (version 13.2) are updated accordingly. The MAH also took the opportunity to bring the product information in line with the QRD template and update the local representatives of the Package Leaflet

15.3.14. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS1180/0047; IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/WS1180/0006; PROCORALAN (CAP) - EMEA/H/C/000597/WS1180/0046

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC with new adverse drug reactions (ADRs): ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. The Package Leaflet and the RMP (version 6) are updated accordingly. In addition, the MAH took the opportunity to align the Product Information in line with the latest QRD template (version 10.0)

15.3.15. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0011/G, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of hepatocellular carcinoma (HCC) based on pivotal study 304: a multicentre, randomized, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib versus sorafenib in first-line treatment of subjects with unresectable HCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 10) are updated accordingly; 2) section 4.2 of the SmPC is updated to add that the

medicinal product can be administered as a suspension in water or apple juice. In addition, the labelling is updated to include an unique identifier

15.3.16. Lumacaftor, ivacaftor – ORKAMBI (CAP) – EMEA/H/C/003954/X/0020

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Extension application (line extension) to add a new strength of film-coated tablets (100 mg lumacaftor/125 mg ivacaftor) for paediatric use from 6 to 11 years of age. The RMP (version 3.1) is updated accordingly

15.3.17. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0128

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 4.6 of the SmPC in order to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women (RMP category 3 study (MEA099)). The RMP (version 15.0) is updated accordingly

15.3.18. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0064/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Grouped variation consisting of: 1) extension of indication for Isentress 100 mg granules for oral suspension to include the treatment of human immunodeficiency virus type 1 (HIV-1) in exposed full-term neonates under the age of 4 weeks based on safety and pharmacokinetic (PK) data from a pivotal phase 1 study IMPAACT P1110 (protocol 080) conducted in a total of 42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and ≥2,000 g), who received either 2 single doses of oral suspension within 48 hours of birth and day 7-10 of age (cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The provision of the results of IMPAACT P1110 study addresses the final paediatric investigation plan (PIP) measure, i.e. study 4, conducted to generate PK, safety, and tolerability data in HIV exposed neonates and infants <6 weeks of age born to HIV infected mothers; 2) update of the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurements of the smaller doses required for neonates. As a consequence, the 5 mL syringe supplied in the current commercial kit is replaced with 3 new oral dosing syringes, and sizes (1 mL, 3 mL, and 10 mL) from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC are updated. The labelling, the instructions for use in the Package Leaflet and the RMP (version 12.0) are updated accordingly

15.3.19. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0060/G, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variation consisting of: 1) extension of indication to include paediatric population for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients from 1 year of age and older. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.3 6.5, 6.6 and 8 of the SmPC are updated accordingly. The RMP (version 18.3) is updated accordingly. Furthermore, the Product information is brought in line with the latest QRD template (version 10); 2) addition of a low-dose romiplostim 125 microgram vial presentation for powder for solution for injection (4 vials pack); 3) addition of a 1 vial pack size of a low-dose romiplostim 125 microgram presentation

15.3.20. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1211/0059; RISTABEN (CAP) - EMEA/H/C/001234/WS1211/0051; TESAVEL (CAP) - EMEA/H/C/000910/WS1211/0059; XELEVIA (CAP) - EMEA/H/C/000762/WS1211/0063

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to modify the information on dosing, an existing warning and administration instructions, respectively for use of sitagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. The RMP (version 8) is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Tesavel and to bring the Product Information in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

15.3.21. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1212/0085/G; JANUMET (CAP) - EMEA/H/C/000861/WS1212/0085/G; RISTFOR (CAP) - EMEA/H/C/001235/WS1212/0072/G; VELMETIA (CAP) - EMEA/H/C/000862/WS1212/0088/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2. and 5.2 of the SmPC in order to modify the information on dosing, and administration instructions respectively for use of sitagliptin/metformin in patients with type 2 diabetes mellitus (T2DM) and moderate renal impairment. The RMP (version 8) is updated accordingly. In addition, section 4.5 of the SmPC is updated to include information on the concomitant use of ranolazine, vandetanib, dolutegravir and cimetidine. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for Efficib and to bring the product information (PI) in line with the latest QRD template (version 10). Minor editorial changes are also introduced in the Product Information

15.3.22. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/II/0065

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on study A6181109: 'a randomized double-blind phase 3 study of adjuvant sunitinib *vs*. placebo in subjects at high risk of recurrent RCC'. The Package Leaflet and the RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and Package Leaflet. This procedure fulfils PAM (FU2 22.5). Furthermore, the product information (PI) is brought in line with the latest QRD template (version 10)

15.3.23. Tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/II/0004

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to provide 96 week data from studies GS-US-320-0108 and GS-US-320-0110, listed as category 3 studies in the RMP. GS-US-320-0108 is an ongoing phase 3, randomized, double-blind, non-inferiority study evaluating the safety and efficacy of Vemlidy 25 mg compared with tenofovir disoproxil fumarate 300 mg in hepatitis B e-antigen (HBeAg)-negative subjects with chronic hepatitis B. GS-US-320-0110 is a an ongoing phase 3, randomized, double-blind, non-inferiority study evaluating the safety and efficacy of Vemlidy versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive subjects with chronic hepatitis B. The Package Leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

15.3.24. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0072

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of juvenile idiopathic polyarthritis (pJIA) rheumatoid factor positive or negative and extended oligoarthritis in patients of 2 years of age and older, who have responded inadequately to previous therapy with methotrexate. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 23.0) are updated accordingly

16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

16.1. PSUR procedures including centrally authorised products only

16.1.1. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201703

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.2. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/201704

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201703

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.4. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201703

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.5. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins - CHONDROCELECT[49] - PSUSA/00000273/201604

Applicant: TiGenix NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUR procedure

[49] EC decision dated 29 July 2016 on the MA withdrawal of ChondroCelect

16.1.1. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201704

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Dimethyl fumarate - TECFIDERA (CAP) - PSUSA/00010143/201703

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.3. Diphtheria, tetanus, pertussis antigens (pertussis toxoid, filamentous haemagglutinin) (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccines (adsorbed) - HEXACIMA (CAP); HEXAXIM (Art 58[50]); HEXYON (CAP) - PSUSA/00010091/201704

Applicants: Sanofi Pasteur SA (Hexacima, Hexaxim), Sanofi Pasteur Europe (Hexyon)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.1. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.3. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[50] Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.4. Entecavir - BARACLUDE (CAP) - PSUSA/00001224/201703

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.5. Ertapenem - INVANZ (CAP) - PSUSA/00001256/201703

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.6. Everolimus[51] - AFINITOR (CAP) - PSUSA/00010268/201703

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.7. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/201703

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.8. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/201704

Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.1.9. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201703

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.10. Florbetapir (^{18}F) - AMYVID (CAP) - PSUSA/00010032/201704

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

[51] Renal cell carcinoma indication only

Scope: Evaluation of a PSUSA procedure

16.1.11. Histamine[52] - CEPLENE (CAP) - PSUSA/00001610/201704

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.12. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201704

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.13. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201703

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.14. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/201704

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.1. Irinotecan[53] - ONIVYDE (CAP) - PSUSA/00010534/201704

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.1. Mannitol[54] - BRONCHITOL (CAP) - PSUSA/00009226/201704

Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[52] Acute myeloid leukaemia indication only
[53] Liposomal formulations only
[54] Cystic fibrosis indication only

16.1.1. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201703

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201704

Applicant: Helsinn Birex Pharmaceuticals Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.1. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201704

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Oestrogens conjugated, bazedoxifene - DUAVIVE (CAP) - PSUSA/00010321/201704

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.1. Para-aminosalicyic acid[55] - GRANUPAS (CAP) - PSUSA/00010171/201704

Applicant: Lucane Pharma

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.2. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201703

Applicant: Bioprojet pharma

[55] Centrally authorised product only

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.1. Regadenoson - RAPISCAN (CAP) - PSUSA/00002616/201704

Applicant: Rapidscan Pharma Solutions EU Ltd.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.2. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201704

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.3. Tacrolimus[56] - PROTOPIC (CAP) - PSUSA/00002840/201703

Applicant: Leo Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.4. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201704

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/201704

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

16.2.1. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201702

Applicants: Clinigen Healthcare Ltd (Savene), various

PRAC Rapporteur: Ghania Chamouni

[56] Topical formulations only

Scope: Evaluation of a PSUSA procedure

16.2.2. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP), VIREAD (CAP); NAP - PSUSA/00002892/201703

Applicants: Mylan S.A.S (Tenofovir disoproxil Mylan), Zentiva k.s. (Tenofovir disoproxil Zentiva), Gilead Sciences International Limited (Viread), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

16.3. PSUR procedures including nationally approved products (NAPs) only

16.3.1. Acetyl salicylic acid, atorvastatin, ramipril (NAP) - PSUSA/00010280/201702

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Amoxicillin (NAP) - PSUSA/00000187/201703

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Amoxicillin, clavulanate (NAP) - PSUSA/00000188/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Bicalutamide (NAP) - PSUSA/00000407/201702

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.5. Clodronic acid (NAP) - PSUSA/00000804/201702

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.6. Cromoglicic acid (NAP) - PSUSA/00000883/201702

Applicant(s): various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.7. Eplerenone (NAP) - PSUSA/00001236/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.8. Fexofenadine (NAP) - PSUSA/00001388/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.9. Fish oil, olive oil, soybean oil, triglycerides medium chain (NAP) - PSUSA/00010223/201702

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.10. Fluconazole (NAP) - PSUSA/00001404/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.1. Frovatriptan (NAP) - PSUSA/00001484/201703

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.3.2. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201703

Applicant(s): various

PRAC Lead: Eva Jirsova

Scope: Evaluation of a PSUSA procedure

16.3.3. Human plasma[57] (NAP) - PSUSA/00001635/201702

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.4. Hydroquinidine (NAP) - PSUSA/00001688/201703

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.1. Influenza vaccine (split virion, inactivated)[58] (NAP) - PSUSA/00010298/201703

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.2. Influenza vaccine (split virion, inactivated, prepared in cell cultures) (NAP) - PSUSA/00010299/201703

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.3. Influenza vaccine (surface antigen, inactivated) (NAP) - PSUSA/00001744/201703

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.3.1. Influenza vaccine (surface antigen, inactivated, adjuvanted) (NAP) - PSUSA/00010300/201703

Applicant(s): various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

[57] Pooled and treated for virus inactivation only
[58] Non-centrally authorised products only

16.3.2. Mannitol[59] (NAP) - PSUSA/00010005/201702

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.3.1. Nabumetone (NAP) - PSUSA/00002101/201703

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.2. Naratriptan (NAP) - PSUSA/00002126/201702

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.3. Pimecrolimus (NAP) - PSUSA/00002411/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.1. Technetium (^{99m}Tc) pertechnetate (NAP) - PSUSA/00002866/201703

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. Triamcinolone[60] (NAP) - PSUSA/00010292/201703

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.3. Zolmitriptan (NAP) - PSUSA/00003150/201703

Applicant(s): various

[59] All indications except cystic fibrosis
[60] Intraocular formulations only

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/LEG 014

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review on severe cutaneous adverse reactions (SCARs) in patients treated with the combination of dabrafenib and trametinib as well as the dabrafenib monotherapy as requested in the conclusions of PSUSA/00010084/201608 adopted in March 2017

16.4.2. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 155

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Summary of available data on response to common vaccines, including pneumococcal vaccines, in patients on Remicade (infliximab) for the different approved indications as requested in the conclusions of PSUSA/00010231/201608 adopted in April 2017

16.4.1. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/LEG 005.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to LEG 005 [detailed review on suicidal ideation and behaviour providing preclinical, clinical, epidemiology and post-marketing data as requested in the conclusions of EMEA/H/C/PSUSA/00010341/201606 adopted by PRAC in January 2017] as per the request for supplementary information (RSI) adopted in June 2017

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)[61]

17.1.1. Blinatumomab – BLINCYTO (CAP) - EMEA/H/C/PSA/S/0024

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsova

Scope: Amendment to a previously agreed protocol for an observational study of blinatumomab safety and effectiveness, utilisation and treatment practices in order to characterise the safety of blinatumomab in routine clinical practice, its effectiveness, medication errors and utilisation [protocol previously adopted within procedure EMEA/H/C/PSP/0041.1 at the September 2016 PRAC meeting]

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[62]

17.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 008.1 including a revised protocol [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in May 2017

17.2.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.1 including a revised protocol [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in May 2017

17.2.3. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 002.2

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

[61] In accordance with Article 107n of Directive 2001/83/EC
[62] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Scope: MAH's response to MEA 002.1 including a revised protocol [PASS protocol for a multiple sclerosis (MS) pregnancy exposure registry study 109MS402 (category 3) aiming at evaluating prospectively pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product] as per the request for supplementary information (RSI) adopted in June 2017

17.2.4. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.3

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's response to MEA 001.2 including a revised protocol [protocol for study I6E-AV-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid reader training programme, initially endorsed by PRAC/CHMP in December 2013, amended following the conclusions of variation II/22 finalised at CHMP in December 2016 to allow the optional use of quantitative reading as an adjunct to visual reading leading resulting in changes in the reader training programme [final clinical study report (CSR) due date: Q4/2017-Q1/2018] as per the request for supplementary information (RSI) adopted in June 2017

17.2.5. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol (version 3) for a non-imposed, non-interventional PASS safety study: a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries (DUS-database) and protocol (version 1) for a prescriber survey (DUS-survey) conducted in European countries

17.2.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 007

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study SB2-G41-AS; SB2-G42-CD: a prospective observational cohort study in ankylosing spondylitis (AS) and Crohn's disease (CD) for two years to observe safety, efficacy and immunogenicity of Flixabi with active comparator in AS and CD (as requested in the initial opinion)

17.2.7. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/MEA 046.2

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to MEA 046.1 including a revised protocol [a PASS protocol to further investigate and characterise the associations of lenalidomide and tumour flare reaction (TFR)/high tumour burden following the extension of indication for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL) (as per the conclusions of variation II/79) (final clinical study report (CSR) planned in December 2022)]

as per the request for supplementary information (RSI) adopted in June 2017

17.2.8. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.3

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 004.2 including a revised protocol [study XM22-ONC-50002: a multi-country, multicentre, retrospective observational study to describe the pattern of lipegfilgrastim use, and specifically to quantify the extent of lipegfilgrastim off-label use in routine clinical practice in several countries of the EU to reflect a revised list of countries] as per the request for supplementary information (RSI) adopted in May 2017

17.2.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.3

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.2 [submission of a draft protocol synopsis for an observational retrospective database study based on secondary data analysis using existing databases, as suitable] as per request for supplementary information (RSI) adopted in May 2017

17.3. Results of PASS imposed in the marketing authorisation(s)[63]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[64]

17.4.1. Dronedarone - MULTAQ (CAP) - EMEA/H/C/001043/II/0039/G

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) submission of the final report from study DRONE_C_05917 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed for the surveillance of serious liver injuries/diseases (SLD) with the use of dronedarone using multiple databases in the US, including the addendum on surveillance of interstitial lung disease (ILD); 2) submission of the final report from study DRONE_C_05911 (listed as a category 3 study in the RMP): a non-interventional epidemiological study aimed at studying the concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy). The RMP (version 11.0) is updated accordingly

[63] In accordance with Article 107p-q of Directive 2001/83/EC
[64] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.2. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1261/0212; LIFMIOR (CAP) - EMEA/H/C/004167/WS1261/0010

Applicant: Pfizer Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final report for the anti-rheumatic treatment in Sweden Registry-etanercept cohort study (listed as a category 3 study in the RMP): a non-interventional PASS aimed at providing an assessment of a number of pre-specified safety outcomes for Enbrel as used in the treatment of rheumatoid arthritis (RA) in Sweden, using data from the Antirheumatic Therapies in Sweden (ARTIS) system, in total and from 2006

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[65]

17.5.1. Albiglutide - EPERZAN (CAP) - EMEA/H/C/002735/MEA 005.4

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Interim report for a phase IV observational drug utilisation and foetal outcome study PRJ2379/201954 (non-interventional cohort, category 3 in the RMP): a retrospective cohort study to assess the utilisation of albiglutide among women of child bearing age in the US

17.5.2. Dalbavancin - XYDALBA (CAP) - EMEA/H/C/002840/MEA 002

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Second interim report for microbial surveillance study 14-DUR-01: Surveillance of dalbavancin resistance tested against clinical isolates collected in the United States and Europe in 2015 to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label for acute bacterial skin and skin structure infection (ABSSSI) and to determine the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin

17.5.3. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/MEA 039.6

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd.

PRAC Rapporteur: Martin Huber

Scope: Fourth annual report for malignant events associated with efavirenz: Diagnostic Consulting Network (DCN) report as a routine risk minimisation measures

[65] In line with the revised variations regulation for any submission before 4 August 2013

17.5.4. Estrogens conjugated, bazedoxifene - DUAVIVE (CAP) - EMEA/H/C/002314/MEA 002.6

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Second interim study report for a US category 3, non-interventional PASS (B2311060 study): active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data as per the request for supplementary information (RSI) adopted in December 2016. This interim report includes data through the second year of CE/BZA availability

17.5.5. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/MEA 014.3

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Fourth interim analysis for study CRAD001MIC03 (TOSCA): a safety sub-study classified as a PASS entitled: 'international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC)'

17.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.6

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Seventh annual report from the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): a long-term observational study of the safety of biologic treatments in rheumatoid arthritis

17.5.7. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 017.10

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Sixth annual interim report on study CA184-143: a multinational prospective, observational study in patients with unresectable or metastatic melanoma to estimate the incidence and severity of adverse reactions in adult patients treated with ipilimumab in the post-approval setting and to describe the management of adverse reactions and their outcomes in ipilimumab-treated patients in the post-approval setting [final clinical study report (CSR) planned in 2017-4Q/2018]

17.5.8. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 013.3

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim yearly report for study No GS-EU-337-1820: a prospective observational on

drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) coinfection

17.5.9. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/SOB 003.3

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Fourth annual report on the Lomitapide Observational Worldwide Evaluation Registry [LOWER] study collecting information on the safety and effectiveness outcomes of patients treated with lomitapide; and Pregnancy Exposure Registry [PER] study collecting data on pregnancies that occur in women exposed to lomitapide at any time within 30 days prior to the first day of the last menstrual period (LMP) prior to pregnancy or during pregnancy

17.5.10. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.5

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: First annual interim report for study VFMCRP-MEAF-PA21-01-EU or 'Velphoro Evaluation of Real-life saFety, effectIveness and adherence (VERIFIE)': a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro in patients with hyperphosphataemia undergoing haemodialysis (HD) or peritoneal dialysis (PD)

17.6. Others

17.6.1. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/REC 001

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Amended protocol for label extension study (R668-AD-1225): an open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials

17.6.2. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/LEG 058.2

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to LEG 058.1 [evaluation of Increlex growth forum database (EU-IGFD) post-marketing surveillance: a multicentre, open-label, non-interventional study based in Europe (ENCEPP/SDPP/7708) collecting long term safety and effectiveness data on mecasermin] as per the request for supplementary information (RSI) adopted in July 2017

17.6.3. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.6

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to MEA 093.5 on the revised statistical analysis plan (SAP) for the RIVAS study [PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS)] as per request for supplementary information (RSI) adopted in June 2017

17.6.4. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 017

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the primary clinical study report (CSR) (MEA 017) for study BO28408 (KRISTINE): a randomized, multicentre, open-label, two-arm, phase 3 neoadjuvant study evaluating trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with human epidermal growth factor 2 (HER2)-positive breast cancer

17.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

17.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

17.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0055 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.1.2. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0067 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.3. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0026 (without RMP)

Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.4. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/S/0029 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.5. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0038 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0024 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Conditional renewal of the marketing authorisation

18.2.2. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0027 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0027 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/R/0021 (without RMP)

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/R/0105 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.3. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXYON (CAP) - EMEA/H/C/002796/R/0072 (with RMP)

Applicant: Sanofi Pasteur Europe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.4. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type B conjugate vaccine (adsorbed) - HEXACIMA (CAP) - EMEA/H/C/002702/R/0068 (with RMP)

Applicant: Sanofi Pasteur SA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.5. Imatinib - IMATINIB ACTAVIS (CAP) - EMEA/H/C/002594/R/0015 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.6. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/R/0037 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.7. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/R/0024 (with RMP)

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18.3.8. Memantine - MEMANTINE MYLAN (CAP) - EMEA/H/C/002660/R/0010 (without RMP)

Applicant: Generics UK Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.9. Memantine - NEMDATINE (CAP) - EMEA/H/C/002680/R/0008 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.10. Memantine hydrochloride - MEMANTINE LEK (CAP) - EMEA/H/C/002630/R/0009 (without RMP)

Applicant: Pharmathen S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.11. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/R/0042 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.12. Telmisartan, hydrochlorothiazide - TOLUCOMBI (CAP) - EMEA/H/C/002549/R/0020 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 23-26 October 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Daniela Philadelphy	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence Defays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in final deliberations and voting on:	3.2.1. Fluoroquinolones for systemic and inhalation use; quinolones for systemic and inhalation use
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations	3.2.1. Fluoroquinolones for systemic and inhalation use; quinolones

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	for systemic and inhalation use; 4.2.1.Levonorgestrel (NAP) 4.3.2.Levonorgestrel (NAP) 6.3.2. Ibuprofen (NAP); ibuprofen, lysine (NAP)
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	3.2.1. Fluoroquinolones for systemic and inhalation use; quinolones for systemic and inhalation use; 3.4.1.Paracetamol modified release (NAP); 11.2.1. Tramadol (NAP)
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Radim Tobolka	Expert - via telephone*	Czech Republic	No interests declared	Full involvement
Torbjorn Callreus	Expert - in person*	Denmark	No interests declared	Full involvement
Jens Ersbøll	Expert - via telephone*	Denmark	No interests declared	Full involvement
Helle Gerda Olsen	Expert - via telephone*	Denmark	No interests declared	Full involvement
Rasmus Heje Thomsen	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Augusto Fernandez	Expert - via telephone*	France	No interests declared	Full involvement
Adrien Inoubli	Expert - via telephone*	France	No interests declared	Full involvement
Maxim Frizler	Expert - via	Germany	No	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		restrictions applicable to this meeting	
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Georgios Papazisis	Expert - via telephone*	Greece	No interests declared	Full involvement
Anna Marie Coleman	Expert - via telephone*	Ireland	No interests declared	Full involvement
Maarten Lagendijk	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Peter Mol	Expert - in person*	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Expert - via telephone*	Norway	No interests declared	Full involvement
Justyna Pilecka	Expert - via telephone*	Poland	No restrictions applicable to this meeting	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Expert - via telephone*	Poland	No interests declared	Full involvement
Mário Miguel Rosa	Expert - in person*	Portugal	No restrictions applicable to this meeting	Full involvement
Blanca Garcia-Ochoa	Expert - in person*	Spain	No interests declared	Full involvement
Almudena Lopez-Fando	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Kristin Elf	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Malcolm Macleaod	Expert - via telephone*	United Kingdom	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Nicola Parkinson	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections
(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:
http://www.ema.europa.eu/em