1 September 2017
EMA/PRAC/631448/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes for the meeting on 3-6 July 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be 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 scopes 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 3-6 July 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 (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.

The PRAC Chair welcomed Eva Jirsová, replacing Jana Mladá, as the new member for the Czech Republic who had so far been the alternate member. In addition, Jana Lukačišinová was welcomed as the new alternate for the Czech Republic. Moreover, Ghania Chamouni was welcomed as the new member for France and Sofia Trantza as the new alternate for Greece.

Finally, the PRAC welcomed the new Estonian presidency of the Council of the EU.

1.2. Agenda of the meeting on 3-6 July 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 6-9 June 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 6-9 June 2017 were published on the EMA website on 27 July 2017 (EMA/PRAC/478147/2017).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

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

Applicant(s): 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 is ongoing for Zinbryta (daclizumab) indicated for the treatment of relapsing forms of multiple sclerosis (RMS) in order to further investigate the risk of liver injury and assess its impact on the benefit-risk balance of the medicinal product. The review was initiated following cases of serious liver injury, including a fatal case of fulminant liver failure. For further background, see PRAC minutes June 2017.

Discussion

The PRAC discussed the assessment reports prepared by the Rapporteurs, heard the MAH in an oral explanation and discussed the need for provisional measures to protect public health, while the review of liver safety is ongoing.

With regard to provisional measures, the PRAC reviewed the preliminary data provided by the MAH on cases of serious liver injury reported since the initial marketing authorisation, in the context of available safety data from clinical trials submitted in support of the initial marketing authorisation in relation to the overall risk of liver injury with daclizumab. The PRAC noted that a fatal case of fulminant liver failure had occurred despite adherence to the terms of the marketing authorisation(s) and the risk minimisation measures recommended, including the regular liver function monitoring. In view of this, and while the magnitude and nature of the risk of liver injury is being further investigated, the PRAC considered that

provisional measures are needed to limit the use of daclizumab.

The PRAC recommended as provisional measures, amendment of the indication of daclizumab to restrict its use to adult patients with highly active relapsing disease despite a previous treatment with at least one disease modifying therapy (DMT) or with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment. In addition, the PRAC recommended, as provisional measures to further minimise the risk of liver injury, to strengthen the current warnings to make clear that all patients should be monitored for signs and symptoms of hepatic injury and that liver function testing should be performed at least monthly, to promptly refer patients to a hepatologist in case of signs or symptoms suggestive of such injury, and that treatment initiation is not recommended in patients with other autoimmune conditions. Caution should also be used when medicinal products of known hepatotoxic potential are used concomitantly. In addition, consideration should be given to discontinuing treatment if an adequate therapeutic response is not achieved.

Summary of recommendation(s)/conclusions

The Committee recommended the variation[1] to the terms of the marketing authorisation(s) for Zinbryta (daclizumab) as a provisional measure, without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004. See EMA press release (EMA/463868/2017) entitled 'EMA restricts use of multiple sclerosis medicine Zinbryta - Restrictions are provisional measures while review of liver safety is ongoing'. The PRAC also agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: On 14 July 2017, the European Commission issued a Commission Decision on the provisional measures. The PRAC assessment report on provisional measures (EMA/453660/2017) was published on the EMA website on 19 July 2017. The PRAC adopted a revised recommendation via written procedure on 9 August 2017 to ensure consistent information is provided across certain sections of the product information. On 29 August 2017, the European Commission adopted accordingly a correction of its decision dated 14 July 2017.

3.2.2. Paracetamol[2] (NAP) - EMEA/H/A-31/1445

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

PRAC Rapporteur: Laurence de Fays; PRAC Co-rapporteur: Ulla Wändel Liminga

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

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of the benefit-risk balance of modified- and prolonged-release paracetamol-containing

[1] Update of SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5 and 4.8. The package leaflet is updated accordingly
[2] Modified release formulations only

medicines, following the recent publication by *Salmonson et al.*[3] of a retrospective pharmacokinetic (PK) and clinical analysis of cases of overdose with modified release paracetamol products. In addition, the procedure includes a review of measures to minimise the risk associated with poisoning with modified- and prolonged-release formulations taking into account the benefit-risk balance for all indications of such modified- and prolonged-release formulations. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes February 2017 and PRAC minutes March 2017.

Summary of recommendation(s)/conclusions

The PRAC discussed the joint assessment report of the Rapporteurs and adopted a third list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/460935/2016 rev.1).

3.2.3. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) - EMEA/H/A-31/1454

Applicant(s): Sanofi-Aventis, various

PRAC Rapporteur: Sabine Straus; PRAC Co-rapporteur: Jean-Michel Dogné

Scope: Review of the benefit-risk balance following notification by France 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 medicinal products containing valproate and related substances indicated for the treatment of bipolar disorder, epilepsy and in some EU Member States for the treatment of migraine, in order to assess the evidence in support of a contra-indication in the treatment of bipolar disorder during pregnancy and in women of childbearing potential who are not on effective contraception, and to review the effectiveness of the current risk minimisation measures (RMMs) across all indications. For further background, see PRAC minutes March 2017 and PRAC minutes June 2017.

Summary of recommendation(s)/conclusions

Further to its decision to hold its first public hearing (see PRAC minutes June 2017) on 26 September 2017 during the PRAC meeting scheduled on 25-29 September 2017[4], the PRAC adopted a summary of the safety concerns (SuSaC) with a list of specific questions on which the public's views would be valuable. The PRAC also adopted a list of questions (LoQ) for a stakeholders' meeting.

Furthermore, the PRAC noted that a contraindication on the use of valproate for bipolar disorder during pregnancy and in women of childbearing potential not using effective contraception was to be introduced in France. The PRAC had been kept aware of this action, which was based on the same data used to trigger its ongoing EU review. PRAC's most recent recommendation (EMEA/H/A-31/1387) is that valproate should never be used in pregnancy or in women of childbearing potential not using effective contraception, unless there is no

[3] Salmonson H., Sjoberg G., Brogren J., Hansson E. The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clinical toxicology. 2016;54:424. Abstract 124, European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) XXXVI International Congress 24-27 May, 2016, Madrid, Spain

[4] Corresponding to the October 2017 PRAC plenary meeting

alternative. Further EU-wide recommendations aiming to ensure the most appropriate use of these medicines in all their indications will be made in the next few months once the PRAC has completed its evaluation. While the review is ongoing, patients who have been prescribed valproate and have any concerns about their medication should discuss them with their healthcare professionals and should not stop their treatment without consultation.

3.3. Procedures for finalisation

3.3.1. Lactose of bovine origin-containing medicinal products[5]: methylprednisolone (NAP) - EMEA/H/A-31/1449

Applicant(s): Pfizer Croatia d.o.o. (Solu-Medrol), various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Nikica Mirošević Skvrce

Scope: Review of the benefit-risk balance following notification by Croatia 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 to be concluded for the review of methylprednisolone-containing medicinal products formulated with lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions. The review was initiated following cases of hypersensitivity reactions, including life-threatening anaphylactic reactions, in patients allergic to cow's milk proteins. A final assessment of the data was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes December 2016, PRAC minutes March 2017 and PRAC minutes June 2017.

Discussion

The PRAC reviewed the totality of the data provided by the MAHs in relation to the risk of serious allergic reactions in patients allergic to cow's milk treated for acute allergic conditions with methylprednisolone-containing products formulated with lactose of bovine origin, as well as data available in EudraVigilance and the literature.

The PRAC considered that, in patients allergic to cow's milk, a risk of serious allergic reactions, including anaphylactic reactions, was associated with IV/IM treatment of acute allergic conditions with methylprednisolone-containing products formulated with lactose of bovine origin. The PRAC noted that data currently available did not allow a safe threshold to be established for milk proteins in lactose of bovine origin used as excipients in methylprednisolone-containing products for IV/IM use in acute allergic conditions. The PRAC concluded that the risk of serious allergic reactions should be minimised through inclusion in the product information of a contraindication in patients allergic to cow's milk and warnings to inform health care professionals and patients of this risk. The PRAC also noted that due to the limitations inherent in the emergency settings in which methylprednisolone-containing products are commonly used, these routine measures may not entirely eliminate the risk. In this regard, the PRAC recommended as a condition to the marketing authorisations that the current formulations shall be replaced with formulations free from cow's milk proteins, within

[5] For intravenous (IV) or intramuscular (IM) use indicated for the treatment of acute allergic reactions only

the agreed timeframe. In the interim, the above risk minimisation in the form of changes to the summary of product characteristics, labelling and package leaflet shall be implemented.

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation to be considered by the CMDh to vary[6] the marketing authorisations for methylprednisolone-containing medicinal products formulated with lactose of bovine origin for intravenous/intramuscular (IV/IM) use in acute allergic conditions. See EMA Press Release (EMA/416655/2017) entitled 'PRAC recommends that injectable methylprednisolone products containing lactose must not be given to patients allergic to cow's milk proteins - Companies to replace all current formulations containing lactose with lactose-free formulations'.

The PRAC also agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'CMDh confirms that methylprednisolone injections containing lactose must not be given to patients allergic to cow's milk proteins – current formulations containing lactose will be replaced with lactose-free formulations' (EMA/443893/2017) representing the position of the CMDh was published on the EMA website on 1 August 2017. The PRAC assessment report (EMA/459263/2017) taken into account by the CMDh in its position was published on 8 August 2017.

3.4. Re-examination procedures[7]

3.4.1. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP)
Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); efmoroctocog alfa – ELOCTA (CAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP); turoctocog alfa – NOVOEIGHT (CAP); simoctocog alfa – NUWIQ (CAP); susoctocog alfa – OBIZUR (CAP) - EMEA/H/A-31/1448

Applicant(s): Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Novo Nordisk A/S (NovoEight), Octapharma AB (Nuwiq), Pfizer Limited (Refacto AF), Swedish Orphan Biovitrum AB (publ) (Elocta), Baxalta Innovations GmbH (Obizur), various

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Caroline Laborde

Scope: Re-examination under Article 32 of Directive 2001/83/EC of the 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

Following the PRAC recommendation adopted at the May 2017 PRAC meeting, to vary the terms of the marketing authorisations[8] for human plasma derived factor VIII- and

[6] Update of SmPC sections 4.3 and 4.4. The package leaflet and labelling are updated accordingly
[7] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[8] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly

recombinant coagulation factor VIII-containing medicinal products, a MAH concerned by this referral procedure conducted under Article 31 of Directive 2001/83/EC, notified EMA of its intention to request a re-examination in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes January 2017, PRAC minutes February 2017 , PRAC minutes March 2017, PRAC minutes May 2017 and PRAC minutes June 2017.

Further to the receipt on 5 July 2017 of the grounds for re-examination from a MAH concerned by this referral procedure, the PRAC initiated on 6 July 2017 a re-examination procedure, expected to conclude at the September 2017 PRAC meeting[9].

Summary of recommendation(s)/conclusions

The PRAC adopted by written procedures on 24 July 2017 a list of questions (LoQ) for the ad-hoc expert group meeting. The PRAC also adopted on 25 July 2017 a revised timetable (EMA/PRAC/471536/2016 Rev. 6) for conducting the review concluding in September 2017 and a list of experts (LoE) for the ad-hoc expert group meeting scheduled on 3 August 2017.

3.4.2. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoversetamide – OPTIMARK (CAP); gadoxetic acid (NAP) - EMEA/H/A-31/1437

Applicant(s): Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Valerie Strassmann

Scope: Re-examination procedure under Article 32 of Directive 2001/83/EC of the review of the benefit-risk balance of GdCA following notification by the European Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

Following the PRAC recommendation adopted at the March 2017 PRAC meeting, to vary the terms of the marketing authorisations for products containing intravenous gadobutrol, gadoteric acid, gadoteridol, and gadoxetic acid and intra-articular gadoteric acid and intra-articular gadopentetic acid, and to suspend the marketing authorisations for products containing gadodiamide, gadopentetic acid, gadobenic acid and gadoversetamide, some of the MAHs concerned by this referral procedure conducted under Article 31 of Directive 2001/83/EC, notified the EMA of their intention to request a re-examination in line with Article 32 of Directive 2001/83/EC. For further background, see PRAC minutes March 2016, PRAC minutes June 2016 and PRAC minutes July 2016, PRAC minutes October 2016, PRAC minutes December 2016, PRAC minutes March 2017, PRAC minutes April 2017, PRAC minutes May 2017 and PRAC minutes June 2017.

Discussion

Following the request for re-examination from some of the concerned MAHs further to the PRAC recommendation adopted during the March 2017 PRAC meeting, the PRAC confirmed it had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure. Notwithstanding this, and given the detailed grounds provided by the

[9] Scheduled on 29 August – 1 September 2017

MAHs, the PRAC carried out a new assessment of the available data in the context of the re-examination including the scientific data underlying these grounds and discussed the conclusions reached by the Rapporteurs. In addition, the Chair of the second ad-hoc expert group meeting held on 19 June 2017 presented to the PRAC the responses to its list of questions.

The PRAC considered that data on product stability, as well as *in vitro* and non-clinical studies, strongly suggest that linear gadolinium-containing contrast agents (GdCAs) release gadolinium from the ligand molecules to a greater extent than macrocyclic agents. Gadolinium has been measured in the brain, both indirectly by studies showing signal intensity increases, and directly by studies measuring gadolinium concentrations with mass spectrometry, including methods that allow localisation in the brain (laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS)) and separation of gadolinium species using gel permeation chromatography coupled with mass spectrometry (GPC-MS). Based on non-clinical data, both linear and macrocyclic agents have the ability to distribute to the brain. However, linear agents are retained and persist for up to one year or longer. Macrocyclic agents show only a transient increase in gadolinium in the brain and undergo early washout.

Although no adverse neurological effects, such as cognitive or movement disorders, have yet been demonstrated to be caused by gadolinium accumulation in the brain, long-term safety data are limited. Harmful effects and potential interaction with disease processes are plausible in view of data supporting dechelation of linear agents *in vivo* and the known toxicity of unchelated gadolinium. Toxicity has been seen in other tissues where it accumulates (including nephrogenic systemic fibrosis (NSF), skin plaques) and in non-clinical data. Gadolinium accumulation has also been reported in a range of other tissues including the liver, kidney, muscle, skin and bone in non-clinical and clinical studies. The evidence strongly suggests a correlation between the potential for release of gadolinium from the ligand and the extent of retention in these tissues and organs. Linear GdCAs are associated with a significant risk of NSF, although current risk minimisation measures appear to be effective based on spontaneous adverse drug reaction reporting. In addition to NSF, there is also evidence that other harmful outcomes are associated with exposure to linear GdCAs, in particular gadolinium-associated skin plaques. Clinical studies, both observational and interventional, to fully address the serious concerns of potential neurological effects are not considered feasible within a reasonable period of time. This is due to the range of potential outcomes of interest, the requirement for long term follow-up, and the heterogeneity of the patient population that undergoes magnetic resonance imaging (MRI).

The PRAC considered options for risk minimisation measures. However, as no specific patient group with less risk of accumulation in the brain or a safe threshold level for retention in the brain could be identified, the restriction of the use of linear GdCAs to certain indications or certain groups of patients was considered not appropriate. The PRAC also concluded that there are practical difficulties for an effective restriction of the number of doses administered during the lifetime of a patient.

The PRAC considered that the risk related to linear intravenous (IV) GdCAs gadobenic acid (in all indications besides liver imaging), gadodiamide, gadopentetic acid and gadoversetamide, taking into account the whole safety profile, including the additional potential risk of harm from brain and other tissues accumulation outweighs the benefits. The PRAC took into account that the linear IV agents, Multihance (gadobenic acid) and Primovist (gadoxetic acid), undergo hepatic uptake, and therefore have clinical utility for imaging poorly vascularised hepatic lesions, especially in the delayed phase imaging, that cannot be adequately studied with agents without hepatic uptake and thus allowing early diagnosis of

potentially life threatening diseases. Therefore, the PRAC considered that the benefits of gadobenic acid and gadoxetic acid outweigh the risks related to these products in the context of liver imaging. In relation to Magnevist (gadopentetic acid) for intra-articular injection, in view of the low dose, the limited potential for repeated exposure for patients and the absence of evidence of brain accumulation, PRAC considered that the benefits of this product outweigh its risks.

In view of the above, the Committee concluded that the benefit-risk balance of medicinal products containing IV gadobutrol, gadoteric acid, gadoteridol, gadoxetic acid, IV gadobenic acid in the indication of liver imaging, intra-articular gadoteric acid and intra-articular gadopentetic acid is favourable subject to agreed changes to the product information.

The Committee recommended the variation to the terms of the marketing authorisations for the intraarticular linear agent containing gadopentetic acid, and the IV linear agents containing gadoxetic acid and gadobenic acid including removal of indications. The Committee also recommended the variation to the terms of the marketing authorisation for the macrocyclic agents containing gadoteridol, gadobutrol, and gadoteric acid.

The Committee also considered that the benefit-risk balance of medicinal products containing IV gadobenic acid (in all other indications than liver imaging), gadodiamide, gadopentetic acid (IV presentation), and gadoversetamide is no longer favourable. Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommended the suspension of the marketing authorisations of the concerned medicinal products.

Summary of recommendation(s)/conclusions

The PRAC adopted a recommendation by a majority[10] to vary[11] the terms of the marketing authorisations for the intraarticular linear agent containing gadopentetic acid, and the intravenous linear agents containing gadoxetic acid and gadobenic acid including removal of indications, to vary[12] also the terms of the marketing authorisation for the macrocyclic agents containing gadoteridol, gadobutrol, and gadoteric acid and to suspend the marketing authorisations of medicinal products containing intravenous gadobenic acid (in all other indications than liver imaging), gadodiamide, gadopentetic acid (IV presentation), and gadoversetamide and adopted a recommendation to be considered by CHMP for an opinion.

The Committee, having considered the data submitted in the procedure was of the opinion that the risk management plan (RMP) for products with a positive benefit-risk balance (except the intra-articular agents) should be revised accordingly and that MAHs should make proposals for conducting a further observational study into the effect of GdCA exposure during pregnancy on pregnancy outcomes.

For lifting the suspension, the PRAC recommended that MAHs should provide evidence for clinically important benefits that are currently not established in an identified population or indication and which outweigh the risks related to the product, or that the product (potentially modified or not) does not undergo significant dechelation and does not lead to retention of gadolinium in tissues, including the brain in humans.

The PRAC considered also that a direct healthcare professional communication (DHPC) would be required to communicate the conclusion of this procedure to HCPs in relevant specialties.

[10] The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[11] Update of SmPC sections 4.1, 4.2, 4.4 and 5.2. The package leaflet is updated accordingly
[12] Update of SmPC sections 4.1 and 4.2. The package leaflet is updated accordingly

See Press Release (EMA/424715/2017) entitled 'PRAC confirms restrictions on the use of linear gadolinium agents - Benefit-risk balance of certain linear gadolinium agents no longer favourable'.

Twenty-seven members voted in favour of the recommendation whilst seven members had divergent views[13]. The Norwegian PRAC member agreed with the recommendation.

Post-meeting note: the press release entitled 'EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans - Recommendations conclude EMA's scientific review of gadolinium deposition in brain and other tissues' (EMA/457616/2017) representing the opinion adopted by the CHMP was published on the EMA website on 21 July 2017.

3.5. Others

None

4. Signals assessment and prioritisation[14]

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. Desloratadine – AERINAZE (CAP), AERIUS (CAP), AZOMYR (CAP), DASSELTA (CAP), DESLORATADINE ACTAVIS (CAP), DESLORATADINE RATIOPHARM (CAP), DESLORATADINE TEVA (CAP), NEOCLARITYN (CAP); loratadine (NAP)

Applicant(s): Merck Sharp & Dohme Limited (Aerinaze, Aerius, Azomyr), Krka, d.d., Novo mesto (Dasselta), Actavis Group PTC ehf (Desloratadine Actavis), Ratiopharm GmbH (Desloratadine Ratiopharm), Teva B.V.(Desloratadine Teva); various

PRAC Rapporteur: Laurence de Fays

Scope: Signal of weight increase in children

EPITT 18906 – New signal

Lead Member State(s): BE

Background

Desloratadine is the active metabolite of loratadine and a non-sedating, long-acting second-generation peripheral histamine H1-receptor antagonist indicated for the relief of symptoms associated with allergic rhinitis and urticaria in adults, adolescents and children over the age of one year (depending on the formulation and the strength).

[13]The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded
[14] 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

Following the publication in Signal[15] of an article[16] by *E.Viola et al*. entitled 'desloratadine, loratadine and weight increase in children', containing summaries of analyses of individual case safety reports in VigiBase, a signal of weight increase in children was identified by the United Kingdom. Belgium confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the findings by *E.Viola et al.*, with 22 paediatric cases (11 for each drug) among 159 reports of weight increase (44 due to desloratadine and 115 due to loratadine respectively), with appetite increased reported alongside weight increase in 3 of the loratadine paediatric cases and two of the desloratadine ones, as well as the additional cases reported in EudraVigilance, the UK data, the FDA labelling and the signal about desloratadine and increase appetite published[17] by the Netherlands Pharmacovigilance Centre Lareb in 2011. The PRAC noted that although some of the cases described in the Signal article were confounded by other medications or by the clinical situation of the patient at the time of the event (e.g. presence of oedema), some well described cases with supportive temporal relationship and positive dechallenge/rechallenge (for both drugs) pointed out to loratadine/desloratadine as the probable causative agent.

Having considered the available evidence in EudraVigilance and in the literature, and the known role of histamine H1 receptors in mediating energy intake and expenditure, the PRAC agreed that the MAHs of loratadine- and desloratadine-containing medicinal products should submit a variation to amend the product information. Nevertheless, the PRAC considered it important to obtain the respective originator MAHs comments on the proposed wording.

Summary of recommendation(s)

- The originator MAHs for loratadine- and desloratadine-containing medicinal products should submit to EMA, within 30 days, their comments on the proposed wording for the requested variation to amend their product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post meeting note: Further to a request from the MAH to extend the submission timelines, the PRAC adopted by written procedure a 30 day-extension of the initial timelines for the submission of the responses. Therefore, the MAH should submit its responses to EMA within 60 days.

4.3. Signals follow-up and prioritisation

4.3.1. Amoxicillin (NAP)

Applicant(s): various

[15] SIGNAL is a newsletter about potential medicines safety issues, known as signals, derived from individual case safety reports in VigiBase. Its distribution is restricted to national centres and regulatory authorities in countries that are members of the World Health Organisation (WHO) programme for international drug monitoring

[16] E.Viola and A.Conforti. desloratadine, loratadine and weight increase in children. SIGNAL April 2017. Uppsala Monitoring Centre (UMC)

[17] Netherlands pharmacovigilance centre Lareb. Lareb Database. Desloratadine and increased appetite. 2011. https://databankws.lareb.nl/Downloads/kwb_2011_3_deslo.pdf

PRAC Rapporteur: Jan Neuhauser

Scope: Signal of drug rash eosinophilia systemic symptoms (DRESS) syndrome

EPITT 18802 – Follow-up to May 2017

Background

For background information, see PRAC minutes May 2017.

The MAH of Amoxil (amoxicillin) replied to the request for information on the signal of drug rash eosinophilia systemic symptoms (DRESS) syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH(s) of amoxicillin-containing medicinal products should submit a variation to amend the product information to include the severe cutaneous adverse reactions as serious and occasionally fatal hypersensitivity reactions in the special warnings and precautions for use, as well as to add DRESS among the undesirable effects with a very rare frequency for skin and subcutaneous tissue disorders.

Summary of recommendation(s)

- The MAH(s) for amoxicillin-containing products should submit, within 60 days, to EMA or to the national competent authorities of the MSs, as applicable, a variation to amend their product information[18].

For the full PRAC recommendation, see EMA/PRAC/406987/2017 published on 07/08/2017 on the EMA website.

4.3.2. Ciprofloxacin (NAP); meropenem (NAP)

Applicant(s): various

PRAC Rapporteur: Jan Neuhauser

Scope: Signal of incompatibility between ciprofloxacin and meropenem when co-administered intravenously leading to possible precipitation

EPITT 18790 – Follow-up to March 2017

Background

For background information, see PRAC minutes March 2017.

The MAHs of the originator medicinal products containing meropenem and ciprofloxacin replied to the request for information on the signal of incompatibility between ciprofloxacin and meropenem when co-administered intravenously leading to possible precipitation, and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, literature and the data provided by the MAHs of the originator medicinal products containing meropenem and ciprofloxacin,

[18] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

the PRAC agreed that a plausible cause of incompatibility and precipitate formation might be the pH difference between the two medications. The information for preventing precipitate formation, given that the label instructions are followed, is adequately reflected in the product information of both originator medicinal products containing ciprofloxacin and meropenem, respectively Ciproxin (ciprofloxacin) and Meronem (meropenem). The MAHs of all other ciprofloxacin- and meropenem-containing medicinal products (solutions for infusion) should submit a variation to align their product information, if appropriate, i.e. to contain the corresponding incompatibilities description.

Summary of recommendation(s)

- The MAHs for ciprofloxacin- and meropenem-containing medicinal products (solutions for infusion) should submit to EMA or to the national competent authorities of the MSs, as applicable, within 90 days, a variation to align their product information[19] to that of the originators' as appropriate.

For the full PRAC recommendation, see EMA/PRAC/406987/2017 published on 07/08/2017 on the EMA website.

4.3.3. Darbepoetin alfa – ARANESP (CAP) - EMEA/H/C/000332/SDA/091; epoetin alfa – ABSEAMED (CAP) - EMEA/H/C/000727/SDA/029, BINOCRIT (CAP) - EMEA/H/C/000725/SDA/028, EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/SDA/030, NAP; epoetin beta – NEORECORMON (CAP) - EMEA/H/C/000116/SDA/055; epoetin theta – BIOPOIN (CAP) - EMEA/H/C/0001036/SDA/022, EPORATIO (CAP) - EMEA/H/C/0001033/SDA/022; epoetin zeta – RETACRIT (CAP) - EMEA/H/C/000872/SDA/046, SILAPO (CAP) - EMEA/H/C/000760/SDA/039, methoxy polyethylene glycol-epoetin beta – MIRCERA (CAP) - EMEA/H/C/000739/SDA/039; NAP

Applicants: Amgen Europe B.V. (Aranesp), Hexal AG (Epoetin Alfa Hexal), Hospira UK Limited (Retacrit), Medice Arzneimittel Pütter GmbH & Co. KG (Abseamed), Roche Registration Limited (Neorecormon, Mircera), Ratiopharm GmbH (Eporatio), Sandoz GmbH (Binocrit), Stada Arzneimittel AG (Silapo), Teva GmbH (Biopoin); various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

EPITT 18846 – Follow-up to February 2017

Background

For background information, see PRAC minutes February 2017.

The MAHs of epoetin-containing medicinal products replied to the request for information on the signal of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and the responses were assessed by the Rapporteur.

Discussion

Having considered the evidence provided by the MAHs of epoetin-containing medicinal products, the PRAC recommended that the MAHs of darbepoetin alfa, epoetin alfa, epoetin

[19] Update of SmPC section 6.2. 'Incompatibilities'

beta, epoetin theta, epoetin zeta and methoxy polyethylene glycol-epoetin beta should submit a variation to amend the product information to add for all epoetin-containing medicinal products a warning on SCARs including SJS and TEN that have been reported in association with epoetin treatment and appropriate precautions for use. The variation should include for all epoetins (with the exception of methoxy polyethylene glycol-epoetin beta which already includes information on SJS and TEN in the product information), SCARs including SJS and TEN as an undesirable effect and for darbepoetin alfa SJS/TEN, erythema multiforme, blistering, and skin exfoliation as undesirable effects with a not known frequency in both chronic renal failure patients and cancer patients. In addition, the MAHs should collaboratively distribute a single direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC and CHMP. The MAH for darbepoetin alfa should lead the preparation and distribution of the direct healthcare professional communication (DHPC).

Summary of recommendation(s)

- The MAHs for epoetin-containing medicinal products should submit to EMA, or to the national competent authorities of the MSs, as applicable, within 60 days, a variation for amending the product information[20] as well as distribute collaboratively a DHPC under the lead of the MAH of Aranesp (darbepoetin alfa).

For the full PRAC recommendation, see EMA/PRAC/406987/2017 published on 07/08/2017 on the EMA website.

4.3.4. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/SDA/012.1

Applicant(s): Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Signal of hepatotoxicity

EPITT 18754 – Follow-up to March 2017

Background

For background information, see PRAC minutes March 2017.

The MAH replied to the request for information on the signal of hepatotoxicity and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including the submissions by the MAH of Xtandi (enzalutamide), the PRAC agreed that currently there is insufficient evidence of hepatotoxicity with Xtandi (enzalutamide). However, given the limitations of the data presented, no satisfactory evaluation could be carried out. Therefore, the MAH should monitor all sources of information for evidence of potential hepatotoxicity of enzalutamide with the help of the SMQ[21] 'hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' and should provide specific updates on events suggestive of hepatotoxicity in future PSURs to enable a proper assessment of the possible hepatotoxicity of enzalutamide. The MAH should include all relevant information and provide the reason(s) to

[20] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[21] Standardised MedDRA (Medical dictionary for regulatory activities) queries (SMQ)

disregard any identified case if applicable. Additionally, the clinical trial cases which were excluded from the review submitted due to their treatment allocation being masked should be included and further analysed within the PSUR following the completion of the trial. The planned end date of this trial should be provided in the next PSUR (data lock point: 30/08/2017). Given the number of cases retrieved with a significant rise in hepatic enzymes, liver enzyme elevations should be further discussed within the next PSUR, together with a proposal to update the product information if deemed relevant.

Summary of recommendation(s)

- The MAH for Xtandi (enzalutamide) should further assess the signal of hepatotoxicity with Xtandi (enzalutamide) in future PSURs to be submitted to EMA including a proposal for amending the product information as deemed relevant.

4.3.5. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/SDA/023.1; BYETTA (CAP) - EMEA/H/C/000698/SDA/043.1

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia

EPITT 18688 – Follow-up to February 2017

Background

For background information, see PRAC minutes February 2017.

The MAH replied to the request for information on the signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia and the responses were assessed by the Rapporteur.

Discussion

Having considered the responses submitted by the MAH of Byetta and Bydureon (exenatide), the PRAC agreed with the MAH's commitment to review the instructions for use (IFU) of exenatide-containing products and submit appropriate recommendations for any improvement. The PRAC considered therefore that no further actions were currently warranted.

Summary of recommendation(s)

- The MAH for exenatide-containing medicinal products should submit to EMA, within Q4 2017, as committed a review of IFU of exenatide-containing products and submit appropriate recommendations for any improvement. The PRAC considered consequently that no further actions were currently warranted.

4.3.6. Fulvestrant - FASLODEX (CAP) - EMEA/H/C/000540/SDA/028

Applicant(s): AstraZeneca UK Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of anaphylactic reactions

EPITT 18832 – Follow-up to March 2017

Background

For background information, see PRAC minutes March 2017.

The MAH replied to the request for information on the signal of anaphylactic reactions and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and the already established causal relationship between fulvestrant and hypersensitivity reactions, the PRAC agreed that anaphylactic reactions should also be included in the product information as undesirable effects of the immune system disorder with an uncommon frequency.

Summary of recommendation(s)

- The MAH for Faslodex (fulvelstrant) should submit to EMA, within 60 days, a variation to amend the product information[22].

For the full PRAC recommendation, see EMA/PRAC/406987/2017 published on 07/08/2017 on the EMA website.

4.3.7. Intravenous (IV) fluids containing electrolytes and/or carbohydrates (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of hyponatremia

EPITT 18631 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAH replied to the request for information on the signal of hyponatremia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, and the known association of hyponatraemia with the administration of intravenous (IV) fluids containing electrolytes and/or carbohydrates, the PRAC agreed that the MAH(s) of IV fluids containing electrolytes and/or carbohydrates should submit a variation to amend the product information according to agreed principles, depending on the presence or not of glucose, and to be further adapted at an individual product level.

Summary of recommendation(s)

- The MAH(s) of IV fluids containing electrolytes and/or carbohydrates containing medicinal products should submit to EMA or to the national competent authorities of the MSs, as applicable, within 180 days, a variation to amend the product information[23].

[22] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[23] Update of SmPC sections 4.2, 4.4, 4.5, 4.6 and 4.8.

For the full PRAC recommendation, see EMA/PRAC/406987/2017 published on 07/08/2017 on the EMA website.

Post-meeting note: during the September 2017 PRAC meeting, further consideration was given (see also PRAC minutes June 2017) for the consultation of the Healthcare Professionals' Working Party (HCPWP). This consultation will be mostly focused on how best to cascade the information on the product information updates as well as to consider additional communication and risk minimisation tools to be used in this case and if they have further suggestions on how to use other systems (namely electronic such as point of care alerts) for future reference. The engagement with HCPs will be organised at the optimal time with the support of an abbreviated assessment report.

4.3.8. Prednisolone (NAP); prednisone (NAP)

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of scleroderma renal crisis

EPITT 18888 – Follow-up to June 2017

Background

For background information, see PRAC minutes June 2017.

The MAH replied to the request for information on the signal of scleroderma renal crisis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence, including from published literature, the PRAC agreed that the MAHs of systemic formulations of prednisolone-containing medicinal products, and prednisone-containing medicinal products in doses which provide a systemic concentration equivalent to more than 15 mg prednisolone daily, should submit a variation to amend the product information to include special warnings and precautions for use in relation to the risk of scleroderma renal crisis as well as to add scleroderma renal crisis among undesirable effects with an unknown frequency. Given that the systemic absorption of prednisolone-containing medicinal products and prednisone-containing medicinal products is expected to be low for topical formulations, systemic concentrations corresponding to more than 15 mg prednisolone daily are considered unlikely and no action was therefore recommended.

Summary of recommendation(s)

- The MAH of systemic formulations of prednisolone-containing medicinal products and prednisone-containing medicinal products in doses which provide a systemic concentration equivalent to more than 15 mg prednisolone daily should submit to EMA or to the national competent authorities of the MSs, as applicable, within 60 days, a variation to amend the product information[24].
- For topical formulations, the systemic absorption of prednisolone-containing medicinal products and prednisone-containing medicinal products is expected to be low. Therefore,

[24] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

systemic concentrations corresponding to more than 15 mg prednisolone daily are unlikely. Therefore, action for these medicinal products is not required.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

See also Annex I 15.1.

5.1.1. Adalimumab –EMEA/H/C/004319

Scope: Treatment of rheumatoid arthritis, axial spondyloarthritis, psoriasis, hidradenitis suppurativa (HS), Crohn's disease, ulcerative colitis and uveitis

5.1.2. Dupilumab - EMEA/H/C/004390

Scope: Treatment of moderate-to-severe atopic dermatitis

5.1.3. Fluticasone furoate, umeclidinium, vilanterol - EMEA/H/C/004781

Scope: Treatment of adult patients with chronic obstructive pulmonary disease (COPD)

5.1.4. Fluticasone furoate, umeclidinium, vilanterol - EMEA/H/C/004363

Scope: Treatment of adult patients with chronic obstructive pulmonary disease (COPD)

5.1.5. Guselkumab - EMEA/H/C/004271

Scope: Treatment of plaque psoriasis

5.1.6. Letermovir - EMEA/H/C/004536, Orphan

Applicant: Merck Sharp & Dohme Limited

Scope, accelerated assessment: Treatment and prophylaxis of cytomegalovirus (CMV) reactivation and disease

5.1.7. Naloxone - EMEA/H/C/004325

Scope: Treatment in emergency use for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression

5.1.8. Neratinib - EMEA/H/C/004030

Scope: Treatment and extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2)-overexpressed, amplified breast cancer

who have received prior adjuvant trastuzumab-based therapy

5.1.9. Padeliporfin - EMEA/H/C/004182

Scope: Treatment of prostate cancer

Background

Previous advice was provided in December 2016, see PRAC minutes December 2016.

5.1.10. Trastuzumab - EMEA/H/C/004323

Scope: Treatment of breast cancer and metastatic gastric cancer

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

See also Annex I 15.2.

5.2.1. Fidaxomicin - DIFICLIR (CAP) - EMEA/H/C/002087/II/0028

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 7) in order to remove the post-authorisation measure (PAM) MEA003 regarding clinical study 2819-CL-2001: an open-label, prospective, interventional study in adult patients who received a second treatment course of fidaxomicin to treat a recurrent *Clostridium difficile* infection (CDI) that developed within 3 months after completion of an initially successful treatment of a primary CDI with fidaxomicin, due to the non-feasibility of the study

Background

Fidaxomicin is a macrocyclic antibiotic indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD).

The PRAC is evaluating a type II variation procedure for Dificlir, a centrally authorised medicine containing fidaxomicin, to update the RMP to remove the post-authorisation measure (PAM) MEA003 regarding clinical study 2819-CL-2001 (an open-label, prospective, interventional study in adult patients who received a second treatment course of fidaxomicin to treat a recurrent *Clostridium difficile* infection (CDI) that developed within three months after completion of an initially successful treatment of a primary CDI with fidaxomicin), due to the non-feasibility of the study. For further background, see PRAC minutes May 2017. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

Summary of advice

- The RMP version 7.0 for Dificlir (fidaxomicin) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable.
- In light of the Rapporteur assessment, the PRAC considered that the 'retreatment study' is not feasible to execute within reasonable timelines and is no longer warranted. The

missing information 'repeated fidaxomicin treatment courses' is no longer considered a safety concern.

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

See also Annex I 15.3.

5.3.1. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0141

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on severe cutaneous conditions including erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) following a request for a cumulative review as per the PRAC signal recommendation dated February 2017 (EPITT 18846). The Package Leaflet and the RMP (version 7) are updated accordingly

See also under 4.3.3.

Background

Darbepoetin alfa is a recombinant erythropoietin indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients as well as for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

The CHMP is evaluating a type II variation procedure consisting of an update of the product information for Aranesp, a centrally authorised product containing darbepoetin alfa, to add a warning on severe cutaneous conditions including erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) further to the PRAC recommendation on a safety signal of severe cutaneous adverse reactions (SCARs) including SJS and TEN. For further background, see PRAC minutes February 2017 as well as under 4.3.3. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP version 7 for Aranesp (darbepoetin alfa) in the context of the variation under evaluation by the CHMP was considered acceptable provided that supplementary information relating to the condition is included before finalisation of the variation procedure by the CHMP.
- The next update of the RMP should implement the provision of a direct healthcare professional communication (DHPC) for the important identified of risk severe cutaneous adverse reaction in the relevant parts of the RMP.

5.3.2. 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 in pregnant women (RMP category 3 study (MEA099)). The RMP (version 15.0) is updated accordingly

See also under 9.6.2.

Background

Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes indicated in adults and children including full term neonates, who present with symptoms typical of influenza, for the treatment of influenza when influenza virus is circulating in the community. Oseltamivir is also indicated in post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community, for the seasonal prevention in individuals one year of age or older under exceptional circumstances, as well as for the post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

The CHMP is evaluating a type II variation procedure for Tamiflu, a centrally authorised product containing oseltamivir, to reflect the final study results from a non-interventional safety study BV29684, which assessed the safety of oseltamivir in pregnant women (RMP category 3 study (MEA099)) in the product information. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. See also under 9.6.2. for further PRAC advice to CHMP.

Summary of advice

- The RMP version 15.0 for Tamiflu (oseltamivir) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that supplementary information relating to the condition is included before finalisation of the variation procedure by the CHMP.
- The PRAC did not support the changes to the RMP related to pregnancy, including terminating the annual review of pregnancy cases.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Blinatumomab - BLINCYTO (CAP) - PSUSA/00010460/201612

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-

cells, and is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Blincyto, a centrally authorised medicine containing blinatumomab, 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 Blincyto (blinatumomab) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'cranial nerve disorders' as an undesirable effect with an uncommon frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should include a thorough assessment of ataxia associated with blinatumomab. In addition, the MAH should provide an analysis of all the cases reporting medication errors, separately for each step of the treatment. The MAH should also provide a list of all adverse events separately for each racial/ethnic group reported cumulatively and in the reporting interval. Finally, the MAH should conduct a cumulative analysis of all cases suggestive of serious infusion reactions in patients treated with blinatumomab.

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. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201612

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Concentrate of proteolytic enzymes enriched in bromelain is a debriding agent indicated for the removal of eschar in adults with deep partial and full-thickness thermal burns.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nexobrid, a centrally authorised medicine containing concentrate of proteolytic enzymes enriched in bromelain, 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 Nexobrid (concentrate of proteolytic enzymes enriched in bromelain) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include serious allergic reactions including anaphylactic reaction as an undesirable effect with an unknown

[25] 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

frequency and to include a warning on hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[26].

- In the next PSUR, the MAH should discuss new information regarding pregnancy, systemic exposure and development of antibodies.

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.

6.1.3. Indacaterol - HIROBRIZ BREEZHALER (CAP); ONBREZ BREEZHALER (CAP); OSLIF BREEZHALER (CAP) - PSUSA/00001730/201611 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Indacaterol is a long-acting beta$_2$-adrenergic agonist indicated for the maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hirobriz Breezhaler, Onbrez Breezhaler and Oslif Breezhaler, centrally authorised medicines containing indacaterol, 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 Hirobriz Breezhaler, Onbrez Breezhaler and Oslif Breezhaler (indacaterol) in the approved indication remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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. Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201612

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Lenalidomide is an anti-neoplastic, anti-angiogenic and pro-erythropoietic immunomodulator indicated for the treatment of adult patients with previously untreated multiple myeloma under certain conditions, as well as indicated in combination for the treatment of multiple

[26] 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

myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Lenalomide is also indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revlimid, a centrally authorised medicine containing lenalidomide, 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 Revlimid (lenalidomide) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the dose modifications in case of drug reaction with eosinophilia and systemic symptoms (DRESS), and to include DRESS as a warning and as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should submit cumulative reviews of cases of retinal damage, glaucoma and acute generalised exanthematous pustulosis, and discuss the need for further updates to the product information if appropriate. In addition, the MAH should submit a cumulative review of the cases of human chorionic gonadotropin (HCG) increased, and discuss the evolution of beta-HCG in each case, as well as a review of literature data, with further discussion on additional action to be taken if appropriate.

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. Lutetium (^{177}Lu) chloride - ENDOLUCINBETA (CAP); LUMARK (CAP) - PSUSA/00010391/201612

Applicant: ITG Isotope Technologies Garching GmbH (EndolucinBeta), I.D.B. Holland B.V. (Lumark)

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Lutetium (^{177}Lu) chloride is a radiopharmaceutical precursor indicated to be used only for the radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with this radionuclide.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of EndolucinBeta and Lumark, centrally authorised medicines containing lutetium (^{177}Lu) chloride, and issued a recommendation on their marketing authorisations.

[27] Update of SmPC sections 4.2, 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of EndolucinBeta and Lumark (lutetium (^{177}Lu)) in the approved indication remains unchanged.
- Nevertheless, the product information should be updated to include warnings in relation to myelosuppression, renal irradiation and haematological disorders, and also to add anaemia, thrombocytopenia, leukopenia and lymphopenia as undesirable effects with a very common frequency as well as a description of dry mouth in association with prostate cancer therapy including Lutetium (^{177}Lu)-labelled radioligands. Therefore, the current terms of the marketing authorisations should be varied[28].
- In the next PSUR, the MAHs should submit a cumulative review on the ongoing signal of hepatotoxicity.

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.

6.1.6. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201701

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults, as monotherapy or in combination with ipilimumab. As monotherapy, nivolumab is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer and of advanced renal cell carcinoma after prior therapy in adults, and for the treatment of adult patients with relapsed or refractory classical Hodgkin's lymphoma under certain conditions. In addition, nivolumab is also indicated for the treatment of squamous cell cancer of the head and neck as well as for the treatment of locally advanced unresectable or metastatic urothelial carcinoma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Opdivo, a centrally authorised medicine containing nivolumab, 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 Opdivo (nivolumab) in the approved indications remains unchanged.

[28] 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

- Nevertheless, the product information should be updated to include Vogt-Koyanagi-Harada syndrome as a warning and an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAH should discuss events of pancytopenia and agranulocytosis. In addition, the MAH should analyse the increased incidence of medication errors.

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.

6.1.7. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201612

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3) and is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA[30]-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lynparza, a centrally authorised medicine containing olaparib, 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 Lynparza (olaparib) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include the undesirable effect 'rash' with a common frequency and 'hypersensitivity' and 'dermatitis' with an uncommon frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[31].
- In the next PSUR, the MAH should update the summary of safety concerns in line with the last version of the approved RMP and discuss any new cases of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML).

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.

[29] Update of SmPC sections 4.4 and 4.8. The package leaflet is not updated. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[30] Breast cancer susceptibility gene
[31] 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

6.1.8. Plerixafor - MOZOBIL (CAP) - PSUSA/00002451/201612

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Plerixafor is a bicyclam derivative, a CXCR4 chemokine receptor antagonist and is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma and multiple myeloma whose cells mobilise poorly.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mozobil, a centrally authorised medicine containing plerixafor, 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 Mozobil (plerixafor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include splenomegaly and splenic rupture as a warning and as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- The MAH should submit to EMA, within 60 days, a cumulative review of all cases of arrhythmia reported from all sources, including clinical trials, spontaneous sources and literature. In addition, the MAH should comment on the need to update the product information.

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.

6.1.9. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201612

Applicant: Incyte Biosciences UK Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

Background

Ponatinib is a protein kinase inhibitor indicated for the treatment of chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) and for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), under certain conditions.

[32] 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 assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Iclusig, a centrally authorised medicine containing ponatinib, 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 Iclusig (ponatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the recommendations for dose modifications for neutropenia and thrombocytopenia that are unrelated to leukaemia, as well as for pancreatic adverse events. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should present further information regarding the follow up of the two cases of drug rash eosinophilia systemic symptoms.

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.

6.1.10. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201612 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Ticagrelor is a direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist indicated in combination with acetylsalicylic acid (ASA) for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brilique, a centrally authorised medicine containing ticagrelor, 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 Brilique (ticagrelor) 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 on the potential interaction of ticagrelor with morphine.
- The MAH should submit a separate variation to update the RMP.
- In the next PSUR, the MAH should review all cases of thrombotic events reported after ticagrelor discontinuation and update the product information as appropriate.

[33] Update of SmPC section 4.2. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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.

6.1.11. Umeclidinium bromide, vilanterol - ANORO (CAP); LAVENTAIR (CAP) - PSUSA/00010264/201612

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Umeclidinium bromide is a long acting muscarinic receptor antagonist and vilanterol is a selective long-acting, beta$_2$-adrenergic receptor agonist. The combination is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Anoro and Laventair, centrally authorised medicines containing umeclidinium bromide/vilanterol, 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 Anoro and Laventair (umeclidinium bromide/vilanterol) in the approved indication remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should submit a review of the new cases of 'chest pain', 'non-cardiac chest pain', 'musculoskeletal chest pain' and 'chest discomfort'.

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.

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

See also Annex I 16.2.

6.2.1. Bosentan - STAYVEER (CAP); TRACLEER (CAP); NAP - PSUSA/00000425/201611

Applicant(s): Marklas Nederlands BV (Stayveer), Actelion Registration Ltd. (Tracleer), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Bosentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stayveer and Tracleer, centrally authorised medicines containing bosentan, and nationally authorised medicines containing bosentan, 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 bosentan-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include interactions between bosentan and tadalafil. In addition, the interaction between bosentan and warfarin, simvastatin, ketoconazole and sildenafil already included in the SmPC should be reflected in the package leaflet. Therefore, the current terms of the marketing authorisations should be varied[34].
- In the next PSUR, the MAHs should submit an updated safety review for drug rash eosinophilia systemic symptoms (DRESS) and other severe cutaneous reactions, and hepatocellular carcinoma. In addition, the MAHs should discuss the need to update the product information regarding 'nausea', 'vomiting' and 'asthenia'.
- The MAHs Actelion Registration Ltd. and Marklas Nederlands BV should submit to EMA, within 90 days, an overview of the educational materials together with the controlled distribution systems implemented at national levels. Furthermore, the effectiveness of each measure in place to minimise any risk should be discussed including whether there is a need to strengthen any of these measures. The MAHs should include a discussion on the need to amend Annex II and the patient card detailed in Annex III.

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. PSUR procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Domperidone (NAP) - PSUSA/00001158/201611

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

[34] Update of SmPC section 4.5 to add interaction between bosentan and tadalafil. The package leaflet is updated accordingly. The package leaflet is also updated to reflect the interactions between bosentan and warfarin, simvastatin, ketoconazole, sildenafil. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Domperidone is a D_2-receptor antagonist indicated for the relief of the symptoms of nausea and vomiting.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing domperidone, 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 domperidone-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to reflect that domperidone may be co-administered with apomorphine in the specific population of patients suffering from Parkinson's disease, as long as all the recommended precautions are fulfilled and the benefits of co-administration of domperidone with apomorphine outweigh the risks. Therefore, the current terms of the marketing authorisation(s) should be varied[35].
- In the next PSUR, the MAHs should provide a discussion on the need to further refine the wording of the product information on nervous system disorders. In addition, the MAHs should provide a detailed review of 'dyspnoea'.

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.

6.3.2. Hydroxycarbamide[36] (NAP) - PSUSA/00009182/201612

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Hydroxycarbamide is an antineoplastic agent indicated for the treatment of malignant disease including chronic myeloid leukaemia. It is also indicated for treatment of cancer of the cervix and other solid tumours in conjunction with radiotherapy.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing hydroxycarbamide, 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 hydroxycarbamide-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.

[35] Update of SmPC sections 4.3, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[36] Centrally authorised product(s) excluded

- In the next PSUR, the MAHs should perform cumulative reviews of secondary malignancy, gastrointestinal ulcers, pyoderma gangrenosum, leucocytoclastic vasculitis/parapsoriasis/hyperkeratosis, photodermatosis, and interstitial lung disease, and provide a plausible mechanism by which these undesirable effects could occur. In addition, the MAHs should propose product information updates if deemed appropriate.

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.

6.3.3. Isotretinoin[37] (NAP) - PSUSA/00010488/201611

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Isotretinoin is a retinoid compound and a vitamin A derivative that is a stereoisomer of all-trans-retinoic acid (tretinoin). It is indicated for the oral treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy. It should not be used for the treatment of prepubertal acne and is not recommended in children less than 12 years of age.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing isotretinoin, 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 isotretinoin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'sexual dysfunction including erectile dysfunction and decreased libido' as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisations should be varied[38].
- In the next PSUR, the MAHs should address all cases associated with exposure during pregnancy, as well as amnesia, depression, suicidal ideation, suicide attempt and completed suicide. In addition, the MAHs should provide cumulative reviews of all cases of gynaecomastia, off-label isotretinoin use in paediatric oncology indications, as well as of the risk of inflammatory bowel disease.

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

[37] Oral formulations
[38] 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-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.3.4. Lenograstim (NAP) - PSUSA/00001839/201610

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Lenograstim is a recombinant human granulocyte colony-stimulating factor (G-CSF) indicated for the reduction of the duration of neutropenia and its associated complications in patients under certain conditions. It is also indicated for the mobilisation of peripheral blood progenitor cells (PBPCs), for both patients and healthy donors.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing lenograstim, 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 lenograstim-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on glomerulonephritis with recommendations to perform urinalysis as part of medical assessment, as well as to include glomerulonephritis and musculoskeletal pain as undesirable effects with an unknown frequency and a very common frequency respectively. Therefore, the current terms of the marketing authorisations should be varied[39].
- In the next PSUR, the MAHs should provide comprehensive safety reviews of cases of thrombosis and of vascular disorders related to neurogenic shock.

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.

6.3.5. Magnesium hydroxide (NAP) - PSUSA/00001926/201610

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

[39] 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

Magnesium hydroxide is a salt with antacid, laxative or purgative activities, indicated for short term symptomatic treatment of constipation and other gastrointestinal conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing magnesium hydroxide, 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 magnesium hydroxide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of hypermagnesemia in children and to add the interaction between magnesium hydroxide and salicylates. In addition, 'abdominal pain' should be included as an undesirable effect with an unknown frequency as well as 'hypermagnesemia' with a very rare frequency. Therefore, the current terms of the marketing authorisations should be varied[40].
- In the next PSUR, the MAHs should provide a cumulative review of cases describing a potential drug-drug interaction (DDI) between magnesium hydroxide and coumarinic anticoagulants. In addition, the MAHs should update the safety concerns to better describe the safety profile of magnesium hydroxide-containing medicinal products.

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. Tixocortol (NAP); chlorhexidine gluconate, tixocortol pivalate (NAP) - PSUSA/00010333/201611

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Tixocortol is an anti-inflammatory corticosteroid indicated for inflammatory and allergic conditions of the rhino-pharynx, allergic rhinitis, acute and chronic congestive rhinitis, and vasomotor rhinitis. It is also indicated for haemorrhagic coloproctitis. Tixocortol pivalate is an anti-inflammatory corticosteroid indicated for inflammatory and allergic vasomotor rhinitis. Chlorhexidine gluconate is a biguanide topical antiseptic, and in combination with tixocortol is indicated as a local adjunctive, anti-inflammatory and anti-bacterial treatment of disorders restricted to the oropharynx.

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

Summary of recommendation(s) and conclusions

[40] Update of SmPC sections 4.4, 4.5 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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tixocortol, chlorhexidine gluconate/tixocortol pivalate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the package leaflet should be updated to better reflect the correct administration route of tixocortol, chlorhexidine gluconate/tixocortol pivalate for intranasal use. Therefore, the current terms of the marketing authorisation(s) should be varied[41].

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 Annex I 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[42]

See also Annex I 17.1.

7.1.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/PSA/S/0019

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsova

Scope: Substantial amendment to the protocol for study 20150136: 'an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices', as previously agreed in the conclusions of procedure EMEA/H/C/PSP/0041.1 adopted by PRAC in September 2016

Background

Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. Blincyto is a centrally authorised medicine containing blinatumomab indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

The obligation to conduct a PASS was imposed as a condition of the marketing authorisation(s) due to very limited clinical trial experience with blinatumomab, in order to characterize the safety of Blincyto (blinatumomab) in routine clinical practice. Blincyto (blinatumomab) effectiveness, medication errors, and utilisation as well as safety and effectiveness of Blincyto (blinatumomab) in specified subgroups of patients are also to be assessed. Of note, the study should also evaluate blinatumomab utilisation in late first

[41] Update of the package leaflet. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

[42] In accordance with Article 107n of Directive 2001/83/EC

relapse patients as requested by CHMP, collecting descriptive safety and clinical response information to further confirm the positive benefit risk ratio. Amendment 1 to the protocol for review by the Committee proposed to allow for the inclusion of non-EU countries into the study (e.g. Switzerland) with an increase of the sample size and sites accordingly, and the amendment of the eligibility criteria clarifying that subjects treated in expanded access and compassionate use programmes, or other observational studies conducted by the MAH in which safety endpoints are analysed, are excluded from 20150136 study. Finally, the information on pregnancy and lactation was removed from data collection requirements as well as from subgroup analysis and will be followed using routine pharmacovigilance only.

Endorsement / Refusal of the protocol

- The PRAC, having considered the amended PASS protocol version 2.0 in accordance with Article 107o of Directive 2001/83/EC, endorsed the protocol for the above listed medicinal product(s).

7.1.2. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Aclatasvir – DAKLINZA (CAP); dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir – ZEPATIER (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritеprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, velpatasvir – EPCLUSA (CAP) - EMEA/H/N/PSP/J/0056

Applicant: Gilead Science International on behalf of the consortium - AbbVie Limited (Exviera, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences International Ltd (Epclusa, Harvoni, Sovaldi), Janssen-Cilag International NV (Olysio), Merck Sharp & Dohme Limited (Zepatier)

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Joint PASS protocol for a prospective, non-interventional study evaluating the risk of early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAAV) therapy compared to HCV-infected patients without previous DAAV therapy during routine clinical care, with previous successfully treated HCC, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438)

Background

Following the completion of the European referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-30/1438) and the European Commission decision dated 23 February 2017, the MAHs were required to conduct a joint PASS to further assess the impact of DAAV treatment on the risk of hepatocellular carcinoma (HCC) recurrence. The PRAC Rapporteur was to be appointed.

Summary of recommendation(s) / conclusions

The PRAC appointed Ana Sofia Diniz Martins as Rapporteur for the PASS procedure.

7.1.3. Levonorgestrel (NAP) - EMEA/H/N/PSA/S/0020

Applicant: Bayer Pharma AG (Jaydess, Luadei)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Substantial amendment to the previously agreed protocol (version 2.2) for EURAS-LCS12 study: a European active surveillance study of LCS-12 (levonorgestrel intra-uterine contraceptive system releasing 12 mcg levonorgestrel/24h *in vitro*), an intra-uterine device (IUD) (Jaydess and Luadei) to investigate whether LCS-12 is associated with an increased risk of unintended pregnancy compared to Mirena and to copper IUDs (previous conclusions of procedure EMEA/H/N/PSA/j/0006.1 adopted by PRAC in September 2016[43])

Background

Levonorgestrel is a progestogen indicated, via an intrauterine device, for contraception and the treatment of menorrhagia.

This study is part of the post approval commitment SE/H/1186/01 to further investigate whether there are differences in unintended pregnancy rates with LSC12 compared to Mirena or copper intra-uterine device (IUD). The initial PASS protocol was endorsed by PRAC on 10 April 2014. This third amendment to the PASS protocol aimed at implementing the advice given by the independent Safety Monitoring and Advisory Council to modify the pre-set recruitment rules between IUDs.

Endorsement / Refusal of the protocol

- The PRAC, having considered the amended protocol version 2.3 in accordance with Article 107o of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives.
- The PRAC recommended that the MAH provide further justification on the impact of restriction of enrolment of control patients in a prospective study on reimbursement and treatment decisions, as well as on the ability to meet the scientific objective of the study. In addition, the MAH is requested to consider recalculating the study power and sample size and should further discuss more specific follow-up of neuropsychiatric adverse events occurring within the study in the context of the ongoing signal procedure concerning neuropsychiatric reactions (signal of anxiety, panic attacks, mood changes, sleep disorders and restlessness) with levonorgestrel-containing intrauterine devices.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[44]

See also Annex I 17.2.

7.2.1. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/MEA 003

Applicant: Roche Registration Limited

PRAC Rapporteur: Sabine Straus

Scope: Protocol for study ML939302 (COVENIS): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and

[43] PRAC meeting October 2016 held on 26-29 September 2016
[44] 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

without brain metastasis with BRAF V600 mutant melanoma under real world conditions (study completion planned in Q4/2020)

Background

Cobimetinib is a reversible, selective, allosteric inhibitor that blocks the mitogen-activated protein kinase (MAPK) pathway and is indicated for oral use for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation in combination with vemurafenib.

As part of the RMP for Cotellic (cobimetinib) the MAH was required to conduct a category 3 study ML29155 (a phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B)) in order to determine the safety and efficacy of Cotellic in combination with vemurafenib, in patients with active melanoma brain metastases. Further to its discontinuation, the ML29155 study was replaced as a category 3 study by an alternative ML39302 study (a non-interventional study to investigate the effectiveness, safety and utilization of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions) in the updated EU RMP version 3.2 for Cotellic (cobimetinib) during the PSUSA procedure (see PRAC minutes March 2017) to address the safety concern 'safety and efficacy of patients with central nervous system (CNS) involvement'. Further to the PRAC recommendation adopted at the March 2017 PRAC meeting, the MAH submitted ML39302 PASS protocol (version 1.1) which was assessed by the Rapporteur.

Summary of advice

- The study protocol for Cotellic (cobimetinib) could be acceptable provided an updated protocol is submitted in accordance to the list of revisions agreed by the PRAC.
- Based on comments raised during the procedure on the efficacy aspects of the protocol, it was noted that the proposed study may not adequately address the missing information 'safety and efficacy in patients with CNS involvement' and that a different study design may be more appropriate. Depending on the assessment of the adequacy of the study to address the primary efficacy objectives and/or on the feasibility of an alternative design, other additional pharmacovigilance activities to address this missing information may need to be considered.

7.3. Results of PASS imposed in the marketing authorisation(s)[45]

7.3.1. 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

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

[45] In accordance with Article 107p-q of Directive 2001/83/EC

by PRAC in March 2017

Background

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for flupirtine-containing medicines (EMEA/H/107i/1363), MAHs were required (Annex IV) as a condition to the marketing authorisations to conduct a PASS to evaluate the effectiveness of the risk minimisation activities. The protocol for this retrospective chart review to evaluate the effectiveness of the risk minimisation measures (RMMs) for the use of flupirtine 100 mg immediate-release capsules in daily practice was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. The results raised concerns about failure of the RMMs as agreed following the referral conclusion and a preliminary analysis in BfArM database has shown that cases of hepatic injury are still being received. For background information, 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, PRAC minutes March 2017. Based on the review of the final report of the non-interventional PASS, the PRAC requested supplementary information in March 2017 (see PRAC minutes March 2017). The PRAC discussed the MAH's response.

Summary of advice

- Based on the review of the final report of the non-interventional PASS and the MAH's response to the request for supplementary information, the PRAC considered that further supplementary information should be requested before a recommendation can be made.
- The PRAC considered that the MAH should provide a full critical appraisal including all available scientific evidence with a focus on hepatotoxicity to justify that the benefit-risk balance for the flupirtine-containing products remains favorable. As appropriate, the MAH should propose any further measures to sufficiently minimize the risk of hepatotoxicity identified with flupirtine-containing products.
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 days-assessment timetable will be applied.
- Finally, the data lock point (DLP) for the next PSUR should be brought forward to 24 October 2017 for all flupirtine-containing products.

Post meeting note: Further to a request from the MAH to extend the timelines for submission, the PRAC adopted by written procedure a 30 day-extension of the initial timelines for the submission of the responses.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[46]

See Annex I 17.4.

[46] 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

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

See also Annex I 17.5.

7.5.1. Data collection on adverse events of anti-HIV[47] drugs (D:A:D) study - PRAC evaluation of D:A:D data merger results

Applicant(s): various

PRAC Representatives: Filip Josephson, Deborah Ashby

Scope: Evaluation of the seventeenth data merger

Background

The PRAC discussed the assessment of the seventeenth and final data merger of the D:A:D[48] study, relating mainly to the relative safety of antiretroviral therapy, performed by the EMA representatives on the Highly Active Antiretroviral Therapy (HAART) Oversight Committee. The ongoing regulatory areas of special interest within the D:A:D study include the association of antiretroviral drug exposure with cardiovascular, renal, end stage liver disease (ESLD) and non-acquired immunodeficiency syndrome (AIDS) cancer endpoints. The seventeenth and final data merger for regulatory purposes forms the conclusion of a long and productive regulatory-academic-industry collaboration which has covered the years of the evolution of the antiretroviral treatment paradigm, addressing concerns about cardiovascular, hepatic, renal safety, as well as concerns on potential carcinogenesis. In this submission, the applicant has summarized the findings over these years, several of which have been of regulatory importance.

For further background, see PRAC minutes March 2013, PRAC minutes July 2013, PRAC minutes September 2014, PRAC minutes September 2015, and PRAC minutes December 2016.

Discussion

The PRAC discussed the various findings relating to the risks under investigation in the cohort. Concerning the particular findings reported in this data merger, data were analysed concerning the association of cumulative exposure to darunavir/ritonavir (DRV/r) and atazanavir/ritonavir (ATV/r) with a composite of cardiovascular events including myocardial infarction, stroke, sudden death and invasive cardiovascular procedures. After adjustment, keeping the factors considered to lie on the causal pathway between protease inhibitors/ritonavir (PI/r) use and cardiovascular disease (CVD) fixed at baseline, cumulative exposure to DRV/r, but not ATV/r, was associated with excess CVD risk. The associations remained consistent for myocardial infarction (MI) and stroke separately; after adjustment for total bilirubin levels (associated with ATV/r use and potentially protective of CVD); and when stratifying for whether DRV/r was used as the first ever PI/r containing regimen or not. Earlier studies, including prior D:A:D analyses, showed that the use of older PIs including indinavir (IDV) and lopinavir (LPV) boosted with RTV(/r) was associated with an excess risk of CVD. As a background, the PRAC noted that DRV/r does not increase low density

[47] Human immunodeficiency virus
[48] D:A:D is a large prospective 'meta-cohort' studying outcomes in patients with HIV infection, most of whom receive antiretroviral therapy

lipoprotein (LDL) or triglycerides substantially more than does ATV/r (*Lennox et al, 2014*[49]). However, in a dedicated substudy of ACTG-5257 study[50] described by *Lennox et al*, carotid intima-media thickness progressed more rapidly in patients randomized to DRV/r compared to ATV/r or raltegravir over 144 weeks (*Stein et al, 2015*[51]). The authors speculate whether the difference may be due to the protective effect of ATV/r induced hyperbilirubinemia. DRV/r is used in two different dosing regimens (800/100 mg once daily (o.d) regimen for most patients and 600/100 mg twice daily (b.i.d) regimen for patients with advanced drug resistance). Thus, the target population for DRV/r differs from that where, e.g. ATV/r is primarily used. Since its introduction, DRV/r has been a major 'salvage' drug, for use in patients with extensive resistance (as opposed to ATV/r). However, it is also used as a first line agent and in patients with less advanced resistance. The D:A:D group reported that risk estimates were not impacted when adjusted for use of DRV/r as a first ever PI/r or otherwise.

Summary of advice

- As the current product information for Prezista (darunavir) includes myocardial infarction and angina pectoris as listed events in the section of undesirable effects, but not stroke, the PRAC advised to request the MAH for Prezista as well as MAHs for other DRV-containing products to ensure that stroke is included in the product information in light of the D:A:D findings and their evaluation, using the relevant regulatory procedure[52].

7.6. Others

See Annex I 17.6.

7.7. 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.

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.

[49] Lennox et al, Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor–sparing antiretroviral regimens for treatment-naïve volunteers infected with human immunodeficiency virus 1 (HIV-1). A randomized, controlled equivalence trial. Annals of Internal Medicine. 2014 American College of Physicians

[50] The ARDENT study: atazanavir, raltegravir, or darunavir with emtricitabine/tenofovir for naive treatment

[51] Stein et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness: acquired immune deficiency syndrome (AIDS) clinical trial group study A5260s. AIDS. 2015 September 10; 29(14): 1775–1783. doi:10.1097/QAD.0000000000000762

[52] For Prezista (darunavir), the MAH agreed to submit the requested reviews in the next PSUR (data lock point (DLP) for darunavir: 23/12/2017)

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 minutes.

9.3. Others

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 minutes.

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

9.4. Safety related variations of the marketing authorisation

None

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

None

9.6. Other requests

9.6.1. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/LEG 033.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of responses, including the CHMP Pharmacogenomics Working Party (PgWP) report dated March 2017, to the proposal of a group of academic and clinical experts put forward to the CHMP and PRAC to review the SmPCs of fluoropyrimidines (Xeloda (capecitabine) and 5-fluorouracil (5FU)) and suggesting that screening for dihydropyriminidine dehydrogenase (DPYD) variants and relevant dose reduction in patients taking fluoropyrimidines could reduce the risk of toxicity in patients with dihydropyrimidine dehydrogenase deficiency

Background

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Xeloda is a centrally authorised medicine containing capecitabine and is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer, and as a first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. It is also indicated in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy as well as in monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

In January 2017, the PRAC provided advice to the CHMP following the assessment of the MAH's response to the literature article by *Hendricks et al.*[53] and further additional literature articles. For further background, see PRAC minutes January 2017. The updated Pharmacogenomics Working Party (PgWP) report was presented to PRAC on the further consideration given to the issue as previously advised and as adopted by the CHMP in May 2017.

Summary of advice

- Based on the PgWP advice, the PRAC supported an amendment to the product information of Xeloda (capecitabine) and intravenous (IV) 5-fluorouracil (5-FU)[54] in terms of advice on dihydropyrimidine dehydrogenase (DPD) deficiency and dihydropyrimidine dehydrogenase gene (DPYD) genotyping.
- In addition, the PRAC advised that the remaining issues should be addressed by the MAHs of Xeloda (capecitabine) and IV 5-FU address through two appropriate lists of questions.
- Finally, the PRAC noted that further changes to the product information of capecitabine and IV 5-FU with regard to genotyping might be needed taking into account newly

[53] Henricks LM, Lunenburg CA, Meulendijks D, Gelderblom H, Cats A, Swen JJ, Schellens JH, Guchelaar HJ. Translating DPYD genotype into DPD phenotype: using the DPYD gene activity score. Pharmacogenomics. 2015;16(11):1277-86
[54] Update of SmPC sections 4.3, 4.4 and 5.2

generated data from on-going studies, e.g. NCT02324452[55], and the latest developments in dosing guidelines.

9.6.2. 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 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

See also under 5.3.2.

Background

Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes indicated in adults and children including full term neonates who present with symptoms typical of influenza for the treatment of influenza when influenza virus is circulating in the community. Oseltamivir is also indicated in post-exposure prevention in individuals of 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community, for the seasonal prevention of influenza in individuals of one year of age or older under exceptional circumstances as well as for the post-exposure prevention of influenza in infants of less than 1 year of age during a pandemic influenza outbreak.

The CHMP is evaluating a type II variation procedure for Tamiflu, a centrally authorised product containing oseltamivir, 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)) in the product information. See also under 5.3.2. for further PRAC advice to CHMP on the necessary updates to the RMP to support this type II variation.

The PRAC was presented the conclusion from the assessment of the final study report of study BV29684 assessing the safety of prenatal exposure to oseltamivir. For further background, see PRAC minutes March 2017. The CHMP requested advice from the PRAC, based on the conclusion that a small risk of congenital heart defects in neonates exposed to oseltamivir during pregnancy could not be completely excluded and the consequent MAH's proposal for update of the product information (PI)[56].

Summary of advice

- Based on the review of the final study report and on the consideration that the results of the study did not allow a conclusive assessment of the potential causal relationship, the PRAC advised a stepwise approach asking firstly some additional questions to the MAH to understand whether there is any possibility for dilution of the late pregnancy findings, and secondly to decide if there is a need to update the PI with the study results and/or

[55] Safety, feasibility and cost-effectiveness of genotype-directed individualized dosing of fluoropyrimidines (M14DPD). EudraCT number: 2014-005064-15. NCT02324452
[56] Update of SmPC section 4.6. No changes are proposed by the MAH for the Package leaflet

with a recommendation for pre-diagnostic testing for pregnant women on the presence of influenza.

9.7. Scientific advice

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

See also under Annex I 20.4.

Other safety issues for discussion requested by the Member States

9.8. Safety related variations of the marketing authorisation

None

9.9. Other requests

9.9.1. Flupirtine (NAP)

Applicant(s): Meda (DUS), Teva (PASS, DUS)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of final study results for 1) a PASS (Teva): a multicentre, non-interventional, retrospective chart review study of patients treated with flupirtine-containing medicinal products in Germany comparing two 6-month periods before and after implementation of the risk minimisation measures (RMM) following the referral procedure for flupirtine-containing products (EMEA/H/A-107i/1363); 2) a drug utilisation study (DUS) (Teva): a retrospective cohort analysis of the IMS disease analyser database for four separate annual time intervals (2012-2015) in Germany before and after implementation of the RMM following the referral procedure; 3) a DUS (Meda) (DE/H/3034/1/II/007): a retrospective DUS conducted in an outpatient setting in Germany using an electronic medical record database (IMS disease analyser) and a prescription database (IMS LRx) to describe prescription behaviour during one time period before and two time periods after the implementation of the risk minimisation measures following the referral procedure

Background

Flupirtine is an analgesic currently indicated for the treatment of acute pain (orally) and for postoperative pain (intravenously). In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for flupirtine-containing medicines (EMEA/H/107i/1363), MAHs were required (Annex IV) as conditions to the marketing authorisations to conduct a PASS to evaluate the effectiveness of the risk minimisation activities, and a drug utilisation study (DUS) to characterise prescribing practices for the medicinal product during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription. Separate studies were conducted by Meda Pharma and by Teva group. While the PASS by Meda Pharma was carried out with German and Portuguese data, all other studies were conducted with German data only. While the reports of the DUS conducted by Meda Pharma and both the PASS and DUS conducted by

the Teva group are currently assessed within national procedures, a protocol for a retrospective chart review by Meda Pharma to evaluate the effectiveness of the risk minimisation measures for the use of flupirtine 100 mg immediate-release capsules in daily practice was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC (see 7.3.1.). For background information, 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.

In the context of the evaluation of the conclusions of the DUS conducted by Meda Pharma and from both the PASS and DUS conducted by the Teva group, Germany (BfArM) requested PRAC advice on its assessment. Despite the fact that different groups of participating physicians were included in the studies, the results of the PASS by Teva and by Meda were considered very similar showing a comparably low degree of prescribers' adherence to the safety restrictions and little improvement over time. In less than 5% of patients all predefined criteria of compliance with the safety restrictions were fulfilled. Extremely low proportions of patients with an adequate frequency of liver function tests were noted in all studies. The PRAC was informed of the conclusion that while the overall number of patients and prescriptions had decreased, those patients that were still prescribed flupirtine seemed to be treated with a high degree of non-compliance with the safety restrictions introduced after the referral.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the Member State's conclusions on the assessments of the PASS (Teva group) and the DUS (Meda GmbH and Teva group) results performed within the national procedures.
- The PRAC also advised the Member States that the conclusions of the assessment for the PASS conducted by Meda (EMEA/H/N/PSR/J/0007) should be applied to the PASS (Teva group) and the DUS (Meda GmbH and Teva group) assessments (see PRAC minutes March 2017 and 7.3.1.).

9.9.2. Lacosamide - DE/H/4720/001-004/DC, DE/H/4726/001-004/DC, DE/H/4830/001-004/DC, DE/H/4831/001-004/DC, DE/H/4832-4834/001-004/DC, DE/H/4835/001-004/DC, DE/H/4841/001-004/DC, DE/H/4842/001-004/DC

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of initial marketing authorisation applications under the decentralised procedure for generic lacosamide-containing medicinal products on request of Germany

Background

Lacosamide is an anticonvulsant drug indicated for mono- and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16-18 years) patients with epilepsy.

The current product information for the originator medicinal product, Vimpat (lacosamide), contains information about a general risk of malformations when using anti-epileptic drugs during pregnancy. To increase knowledge about this risk, the RMP (version 11.1) for Vimpat (lacosamide) includes participation of the MAH (and its sponsorship) in the European register

of antiepileptic drugs and pregnancy (EURAP), and possible follow-activities relating to children exposed in utero as additional pharmacovigilance activities (category 3 study).

In the context of multiple generic applications for different MAHs, Germany (BfArM) requested PRAC advice on its position on aligning the generic medicinal products with the originator medicinal product.

Summary of advice

- Based on the review of the available information, the PRAC agreed that the RMP of a generic medicinal product containing lacosamide should follow the originator RMP.
- The PRAC recommended participation of the MAHs/applicants for generic medicinal product containing lacosamide in the EURAP registry.

9.9.3. Levonorgestrel[57] (NAP)

Applicant(s): Bayer (Mirena, Jaydess)

PRAC Lead: Martin Huber

Scope: PRAC consultation on the evaluation of cumulative reviews on levonorgestrel IUS and possible interaction with lamotrigine, the risk of arthralgia and the risk of breast discharge, as requested in the conclusions of procedure PSUSA/00001856/201412, adopted in September 2015

Background

Levonorgestrel is a second-generation progestin (synthetic progesterone) indicated as a hormonal contraceptive, alone or in combination. Furthermore, levonorgestrel is indicated for emergency contraception, for the treatment of heavy menstrual bleeding and protection from endometrial hyperplasia during oestrogen replacement therapy.

As a conclusion of the PSUSA procedure evaluation (see PSUSA/00001856/201412, PRAC minutes September 2015), the MAH for Mirena and Jaydess were required 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 provided cumulative reviews, Germany (BfArM) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed with the assessment and conclusions on the cumulative reviews and advised that no further regulatory action was to be taken at this stage but to closely monitor cases concerning pregnancy and cases of seizures in patients with levonorgestrel IUS who concomitantly receive lamotrigine, and provide a discussion on these cases within the next levonorgestrel PSUR (data lock point (DLP): 23/12/2017).
- Moreover, the PRAC agreed with the proposed list of questions and the request for additional data to be addressed by the MAH within 60 days, with regard to the risk of arthralgia and the risk of breast discharge.

[57] Intrauterine system (IUS) only

10. Organisational, regulatory and methodological matters

10.1. Mandate and organisation of the PRAC

10.1.1. PRAC Brexit ancillary working group

PRAC lead: Almath Spooner

At the organisational matters teleconference on 20 July 2017, the chair of the PRAC ancillary working group on Brexit preparedness reported to PRAC from the second group meeting that took place on 30 June 2017 as well from the first cross-Committee EMA 'Working Group on Committees' operational preparedness for human medicines' meeting held in the margins of the July 2017 PRAC plenary meeting.

10.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals

PRAC lead: Martin Huber, Menno van der Elst, Tatiana Magalova, Albert van der Zeijden, Marianne Lunzer, Jan Neuhauser, Ulla Wändel Liminga

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference held on 20 July 2017 on quantitative measures collected for the second 2017 quarter of PRAC meetings. For previous update, see PRAC minutes April 2017.

10.2. Coordination with EMA Scientific Committees or CMDh

10.2.1. Advanced therapy medicinal products (ATMP) - Revision of procedural advice on the evaluation of ATMP in accordance with Article 8 of Regulation (EC) No 1394/2007

The topic was deferred to September 2017.

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

None

10.4. Cooperation within the EU regulatory network

10.4.1. European Network Training Centre (EU NTC) - operation of pharmacovigilance in the EU training needs and priorities

PRAC lead: Dolores Montero Corominas

As a follow-up to the last PRAC discussion on the European Network Training Centre (EU

NTC) training needs and priorities in relation to operation of pharmacovigilance in the EU (see PRAC minutes June 2017) where a three-year training plan including topic prioritisation, was supported, the EMA Secretariat[58] presented an update on the training plan at the organisational matters teleconference held on 20 July 2017. PRAC members were invited to review the proposed training teams composed of EMA and NCA representatives and express interest in joining the different training teams. Follow-up will be provided in due course.

10.4.2. Innovative Medicines Initiative (IMI) WEB-Recognising Adverse Drug Reactions (WEB-RADR) project – Pharmacovigilance and social media – Work package 1: policy and governance deliverable

PRAC lead: June Raine

At the organisational matters teleconference held on 20 July 2017, the EMA Secretariat presented to PRAC, together with relevant National Competent Authorities' (NCA) representatives, the objectives of the ongoing Innovative Medicines Initiative (IMI) WEB-Recognising Adverse Drug Reactions (WEB-RADR) project, specifically work package 1 on 'policy and governance', including the role of social media as pharmacovigilance tools and as an additional data source. The PRAC was also presented with some proposed regulatory recommendations and provided some feedback. A further update will be provided in due course.

10.5. Cooperation with International Regulators

None

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

None

10.7. PRAC work plan

10.7.1. PRAC work plan for 2017 - update

PRAC lead: June Raine

The topic was deferred to September 2017.

10.8. Planning and reporting

10.8.1. 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 20 July

[58] On behalf of the training curriculum steering group of the 'operation of pharmacovigilance in the EU' (EU PVOP-SG)

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 April 2017.

10.8.2. Marketing authorisation applications (MAA) expected for 2017 – Q2 2017 update

The EMA Secretariat presented, at the organisational matters teleconference held on 20 July 2017, for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see PRAC minutes April 2017.

10.8.3. PRAC workload statistics – Q2 2017

The EMA secretariat presented, at the organisational matters teleconference held on 20 July 2017, quarterly figures to estimate 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 April 2017.

10.9. Pharmacovigilance audits and inspections

10.9.1. Pharmacovigilance systems and their quality systems

None

10.9.2. Pharmacovigilance inspections

None

10.9.3. Pharmacovigilance audits

None

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

None

10.10.1. Periodic safety update reports

None

10.10.2. 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.

10.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version July 2017 reflecting the PRAC's comments impacting on the data lock points (DLP) and PSUR submission frequencies of the different 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 July 2017, the updated EURD list was adopted by the CHMP and CMDh at their July 2017 meetings and published on the EMA website on 21/07/2017, 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)

10.11. Signal management

10.11.1. Good Pharmacovigilance Practice (GVP) module IX on Signal management – revision 1 and addendum

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 20 July 2017, the EMA Secretariat presented to PRAC draft revision 1 of GVP module IX on 'signal management' and addendum I on 'methodological aspects of signal detection from spontaneous reports of suspected adverse reactions' following the public consultation held at the end of 2016 (for further background before public consultation, see PRAC minutes April 2016) and taking into account in particular the recent PRAC discussion on the handling of MAHs' signals after the go-live of the new EudraVigilance (EV) system in November 2017 (see PRAC minutes May 2017).

The PRAC noted the transitional arrangements agreed by the European Commission (EC) regarding the requirements for MAHs to monitor EV data and inform forthwith EMA and NCAs of validated signals. These transitional arrangements for MAHs will enter into force on 22 February 2018 (i.e. three months after the new EV go-live) and will apply for a pilot period of one year, to active substances contained in products subject to additional monitoring.

The PRAC discussed several aspects, such as the tracking of EudraVigilance (EV) signals in variations and PSURs, and possible communication of non-confirmed signals. The PRAC noted that PRAC SMART, CHMP, CMDh, CAT, Pharmacovigilance Inspectors Working Group (PhV IWG) and EudraVigilance Expert Working Group (EV-EWG) were also consulted on the consolidation of revision 1 of GVP module IX and addendum I. As next steps, following a review by EMA Secretariat and the European Commission (EC), the documents will be due

for adoption at PRAC in September 2017.

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

PRAC lead: Sabine Straus

The SMART working group meeting dated 3 July 2017 was cancelled.

10.12. Adverse drug reactions reporting and additional reporting

10.12.1. Guideline on detection and management of duplicate individual cases and individual case safety reports (ICSRs) – revision 1

At the organisational matters teleconference held on 20 July 2017, the EMA Secretariat presented to PRAC 'GVP module VI - Addendum I on duplicate management of suspected adverse reaction reports' corresponding to revision 1 of the existing CHMP guideline on 'detection and management of duplicate individual cases and individual case safety reports (ICSRs)' previously agreed in 2009 before the entry into force in 2012 of the EU legislation on pharmacovigilance. This revision includes an alignment with revision 2 of GVP Module VI (see under 12.12.2.), an update on electronic reporting modalities of ICSRs in the new ICH-E2B(R3) format, an update in line with the revised pharmacovigilance legislation as regards the roles and responsibilities of the EMA, EU NCAs as well as MAHs in relation to the operation of duplicate detection and management of reports of suspected adverse reactions. It also includes some guidance on how to inform the EMA of suspected duplicates in EudraVigilance and changes for consistent presentation of GVP documents. The PRAC adopted GVP module VI - Addendum I. As next steps, the revised GVP module VI is due for agreement by the EU Network Pharmacovigilance Oversight Group (EU-POG) and adoption by the EMA executive director before coming into force.

Post meeting note: On 2 August 2017, GVP module VI Addendum I on 'duplicate management of suspected adverse reaction reports' was published on the EMA website (EMA/405655/2016) and will come into force on 22 November 2017.

10.12.2. Good Pharmacovigilance Practice (GVP) module VI on Collection management and submission of reports of suspected adverse reactions to medicinal products - revision2

As a follow-up to the June 2017 PRAC discussion on the revised GVP module VI on 'Collection management and submission of reports of suspected adverse reactions to medicinal products' (see PRAC minutes June 2017), the PRAC adopted revision 2 of GVP module VI. As next steps, the revised GVP module VI is due for agreement by the EU Network Pharmacovigilance Oversight Group (EU-POG) and adoption by the EMA executive director before coming into force.

Post meeting note: On 2 August 2017, GVP module VI revision 2 was published on the EMA website (EMA/873138/2011 Rev 2*) and will come into force on 22 November 2017.

10.12.3. Management and reporting of adverse reactions to medicinal products

None

10.12.4. Additional monitoring

None

10.12.5. 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 26/07/2017 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

10.13. EudraVigilance database

10.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project – update

As agreed in June 2017 (see PRAC minutes June 2017), the EMA Secretariat provided PRAC at the organisational matters teleconference held on 20 July 2017 with further updates on the EudraVigilance auditable requirement project. The EMA Secretariat presented a communication plan, developed with the Pharmacovigilance Business Team that sets out important milestones as part of the go-live of the new EudraVigilance System on 22 November 2017. It identifies the impacted stakeholders, their needs and interests and determines the communication channels with these stakeholders and the date/frequency of communication. The PRAC adopted the communication plan by written procedure on 24 July 2017. A further update will be given in September 2017 with the main focus on the EudraVigilance go-live strategy.

10.14. Risk management plans and effectiveness of risk minimisations

10.14.1. Risk management systems

None

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

None

10.15. Post-authorisation safety studies (PASS)

10.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

10.16. Community procedures

10.16.1. Referral procedures for safety reasons

None

10.16.2. Referral procedures - pilot phase for implementation of electronic signatures for divergent positions

At the organisational matters teleconference held on 20 July 2017, the EMA Secretariat presented to PRAC a proposal to implement an electronic process for the endorsement of divergent signatures, i.e. to terminate the need for physical signatures from the divergent position documents. The PRAC agreed with the implementation from the September 2017 PRAC meeting of a pilot phase for the replacement of physical signatures for divergent positions for referral procedures with electronic signatures, before this goes live as of the October 2017 PRAC meeting if the pilot is successful.

Post-meeting note: at the September 2017 PRAC meeting, the pilot phase was completed satisfactorily.

10.17. Renewals, conditional renewals, annual reassessments

None

10.18. Risk communication and transparency

10.18.1. Public participation in pharmacovigilance

None

10.18.2. Safety communication

None

10.19. Continuous pharmacovigilance

10.19.1. Incident management

None

10.20. Others

10.20.1. Industry stakeholder platform on the operation of the EU pharmacovigilance – Feedback from the eleventh industry stakeholder platform meeting held on 2 June 2017

At the organisational matters teleconference held on 20 July 2017, the EMA Secretariat provided PRAC with feedback from the eleventh industry stakeholder platform meeting on the operation of EU pharmacovigilance hosted by EMA on 2 June 2017. As part of the topics discussed at the meeting, updates were presented and discussed on the current status of good pharmacovigilance practices (GVP) and on the new signal management process in the EU once the requirement for MAHs to monitor EudraVigilance and to report validated signals is implemented after the go-live of EudraVigilance in November 2017. Further details are available in the highlights from the 11th EMA Industry Platform meeting on the operation of EU pharmacovigilance legislation.

11. Any other business

None

12. Annex I – Signals assessment and prioritisation[59]

12.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria under evaluation 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[60].

12.1.1. Ritonavir - NORVIR (CAP); lopinavir, ritonavir – KALETRA (CAP); levothyroxine (NAP)

Applicant(s): AbbVie Ltd. (Kaletra, Norvir), various

PRAC Rapporteur: Menno van der Elst

[59] 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

[60] 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

Scope: Signal of interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism

EPITT 18896 – New signal

Lead Member State(s): FR, NL

12.1.2. Tofacitinib – XELJANZ (CAP)

Applicant(s): Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Signal of angioedema

EPITT 18904 – New signal

Lead Member State(s): NL

13. Annex I – Risk management plans

13.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

13.1.1. Buprenorphine, naloxone - EMEA/H/C/004407

Scope: Treatment for opioid drug dependence

13.1.2. Carmustine - EMEA/H/C/004326

Scope: Treatment of brain tumours, multiple myeloma, Hodgkin's and non-Hodgkin’s lymphomas

13.1.3. Ritonavir - EMEA/H/C/004549

Scope: Treatment of human immunodeficiency virus 1 (HIV-1)

13.1.4. Tacrolimus - EMEA/H/C/004435

Scope: Treatment of allograft rejection and prophylaxis of transplant

13.2. 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).

13.2.1. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS1169/0028; Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS1169/0032

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMPs for Exviera (version 3.0) and Viekirax (version 3.0) following the CHMP opinion dated 15 December 2016 (EMA/CHMP/847450/2016) on the procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAs) indicated for the treatment of hepatitis C (interferon-free) in order to implement 'hepatitis B reactivation' as an important identified risk, 'emergence of hepatocellular carcinoma' and 'recurrence of hepatocellular carcinoma' as important potential risks, 'patients with previous hepatocellular carcinoma (HCC)' as missing information. The requested studies have also been reflected in the RMPs accordingly

13.2.2. Dapagliflozin – EBYMECT (CAP)- EMEA/H/C/004162/WS1198/0022; EDISTRIDE (CAP) - EMEA/H/C/004161/WS1198/0017; FORXIGA (CAP) - EMEA/H/C/002322/WS1198/0037; XIGDUO (CAP) - EMEA/H/C/002672/WS1198/0033

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMPs for Ebymect (version 13.3), Edistride (version 13.3), Forxiga (version 13.3), Xigduo (version 13.3) following the finalisation in February 2017 (EMEA/H/A-20/1442) of the procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputations

13.2.3. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/II/0129

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 9.0) in order to upgrade the important potential risk 'immunogenicity/safety risk associated with the formation of neutralising antibodies' to an important identified risk

13.2.4. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0049

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 17) in order to amend the study objectives and

milestones for two studies: 1) study CA184332 (a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy in a community setting, a category 3 study in the RMP (MEA 029): to submit the final study report with 2-years of follow-up); 2) study CA184338 (a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy, a category 3 study in the RMP (MEA 030): to submit the final study report with 4-years of follow-up)

13.2.5. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1163/0051; Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1163/0041

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of the RMPs for Harvoni (version 6.0) and Sovaldi (version 6.0) following the CHMP opinion dated 15 December 2016 (EMA/CHMP/847450/2016) on the procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAs) indicated for the treatment of hepatitis C (interferon-free) in order to implement 'hepatitis B reactivation' as an important identified risk, 'emergence of hepatocellular carcinoma' and 'recurrence of hepatocellular carcinoma' as important potential risks, 'patients with previous hepatocellular carcinoma (HCC)' as missing information. The requested studies have also been reflected in the RMPs accordingly

13.2.6. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/II/0020

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 3) and submission of an amended protocol for PASS study NN7008-3553 (a multicentre non-interventional study of safety and efficacy of turoctocog alfa (rFVIII) during long-term treatment of severe and moderately severe haemophilia A (FVIII =<2%), a category 3 study in the RMP) to update the milestone timelines in order to integrate the required additional pharmacovigilance activities, which include a change in the last patient last visit (LPLV) date and a change in the clinical trial report (CTR) finalisation date. In addition, the duration of the trial has been amended from 4 to 7 years

13.3. 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).

13.3.1. Abiraterone acetate - ZYTIGA (CAP) - EMEA/H/C/002321/II/0047

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the treatment of newly diagnosed high risk

metastatic hormone sensitive prostate cancer and in combination with androgen deprivation therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 14.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

13.3.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0163

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of chronic non-infectious uveitis in paediatric patients. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 13.0) are updated accordingly. In addition, the MAH took the opportunity to implement an alternative format statement for blind/partially sighted patients into the Package Leaflet as introduced with procedure EMEA/H/C/000481/N/0155. Furthermore, the MAH made some editorial changes to the package leaflet

13.3.3. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/II/0017

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety and long term use information in the posology following final results from study CAMMS03409: an extension protocol for multiple sclerosis (MS) patients who participated in Genzyme-sponsored studies of alemtuzumab to evaluate the long term safety and efficacy of alemtuzumab in MS patients who received alemtuzumab during prior company-sponsored studies. The Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10.0) and to introduce editorial corrections

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

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Torbjorn Callreus

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

13.3.5. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0006, Orphan

Applicant: GlaxoSmithKline Trading Services, ATMP[61]

PRAC Rapporteur: Sabine Straus

Scope: Quality - sections 4.3 and 4.4 of the SmPC are updated. The RMP (version 1.6) is updated accordingly. The MAH took the opportunity to introduce some editorial changes in Annex II and III-B of the product information

13.3.6. Baricitinib – OLUMIANT (CAP) – EMEA/H/C/004085/II/0001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of section 4.4 of the SmPC in order to add a warning on venous thromboembolism based on analyses of the occurrence of venous thromboembolic events in clinical trials with baricitinib. The Package Leaflet and the RMP (version 2.0) are updated accordingly

13.3.7. Bortezomib - BORTEZOMIB ACCORD (CAP) - EMEA/H/C/003984/X/0008

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Line extension application to add a new strength of powder for solution for injection (1 mg) to the currently approved strength (3.5 mg) of Bortezomib Accord. The RMP (version 6.0) is updated accordingly

13.3.8. 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

13.3.9. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0142

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Valerie Strassmann

[61] Advanced therapy medicinal product

Scope: Extension of indication to include the treatment of anaemia in adult patients with low transfusion demand in low or intermediate-1-risk myelodysplastic syndromes for Aranesp. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to introduce QRD editorial changes in the SmPC, Annex III-A and Annex III-B

13.3.10. 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

13.3.11. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/II/0026

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include paediatric patients from 6 to less than 12 years of age, with body weight of at least 25 kg, infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of paediatric study GS-US-292-0106 (cohort 2): a phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment naive adolescents and virologically suppressed children. The Package Leaflet and the RMP (version 3) are updated accordingly

13.3.12. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/X/0029

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Line extension to add new pharmaceutical form and strengths (film-coated tablets 40 mg and 80 mg) to the currently approved presentations for Xtandi. The RMP (version 10.1) is updated accordingly

13.3.13. Human normal immunoglobulin - PRIVIGEN (CAP) - EMEA/H/C/000831/II/0119

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.8 and 5.1 to implement the results of the PATH

(IgPro20_3003) study results: a randomised, multicentre, double-blind, placebo-controlled, parallel-group phase 3 study to investigate the efficacy, safety, and tolerability of two different doses of IgPro20 (subcutaneous immunoglobulin) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). In addition, the MAH took the opportunity to implement a clarification on the hyperprolinemia types in section 4.3 and to introduce some editorial changes to section 5.2 of the SmPC. The package leaflet and the RMP (version 5.0) are updated accordingly

13.3.14. 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 (re-versal 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)

13.3.15. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0008, Orphan

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the clinical study report (CSR) for study E7080-J081-208: a phase 2 multicentre, open-label, single-arm study to evaluate the safety of once daily oral administration of lenvatinib (E7080) in subjects with advanced thyroid cancer

13.3.16. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0020

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

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

13.3.17. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0016

Applicant: Sunovion Pharmaceuticals Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final clinical study report (CSR) for study D1001057: an extension of study SM-13496 (lurasidone): a phase 3, randomised, double-blind, parallel-group, placebo-controlled, confirmatory study evaluating the long-term safety and efficacy of

lurasidone (40 mg/day or 80 mg/day) in patients with schizophrenia. The RMP (version 5.0) is updated with information relative to this study and information relative to study D1050301 already assessed in P46/006

13.3.18. Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0056, Orphan

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the eighth Niemann-Pick type C (NPC) registry report and update of Annex II-D of the product information to delete the NPC Registry listed as an obligation to the marketing authorisation. The RMP (version 12.1) is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes and bring the Product Information and Annex A in line with the latest QRD template (version 10)

13.3.19. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0016

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final clinical study report (CSR) for study Aura 17: a phase 2, open label, single-arm study to assess the safety and efficacy of AZD9291 in Asia pacific patients with locally advanced/metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutation within the epidermal growth factor receptor gene). The RMP (version 7.0) is updated accordingly

13.3.20. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/X/0008

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Line extension application to add a new pharmaceutical form, powder for solution for injection/infusion (750 U/mL). The RMP (version 2.0) is updated accordingly

13.3.21. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0091

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include paediatric patients from 3 to less than 18 years of age with chronic hepatitis B in the immune-active phase for Pegasys. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from study YV25718: a phase 3b parallel group, open label study of pegylated interferon alfa-2a monotherapy compared to untreated control in children with HBeAg positive chronic hepatitis B. The Package Leaflet and the RMP (version 8.0) are updated accordingly

13.3.22. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0029

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for a non-clinical study 'anti-murine PD-1 antibody (muDX400 L-005571333): an exploratory multiple-dose subcutaneous immunotoxicity study in mice with hepatitis B vaccine (L-005552770)'. The RMP (version 11.0) is updated accordingly

13.3.23. Plerixafor - MOZOBIL (CAP) - EMEA/H/C/001030/II/0032, Orphan

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to reflect the results of the completed study MSC12830 (MOZ11809): 'a phase 4, multicentre, randomised, comparator trial evaluating the standard weight-based dose (0.24 mg/kg) compared to a fixed dose (20 mg) of plerixafor injection in combination with granulocyte-colony stimulating factor (G-CSF) to mobilise and collect ≥5 x 10^6 $CD34^+$ cells/kg in ≤4 days and to evaluate the difference in total systemic exposure in patients with non-Hodgkin's lymphoma weighing ≤70 kg' listed as a category 3 study in the RMP. The Package Leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet

13.3.24. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/II/0117

Applicant: GSK Biologicals SA

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to reflect the results from study 10PN-PD-DIT-072: a phase 3, open, controlled, multicentric study to evaluate the immunogenicity, safety and reactogenicity of Synflorix in children at an increased risk of pneumococcal infection. The Package Leaflet and the RMP (version 16) are updated accordingly. This submission fulfills the post-authorisation measure MEA 065

13.3.25. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/II/0024

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPC in order to include information on the use of rilpivirine in combination with a background regimen for the treatment of human immunodeficiency virus (HIV)-1 infection during pregnancy and postpartum, without dose adjustment following final results from study TMC114HIV3015 (a single arm, open-label trial to assess the pharmacokinetics of darunavir/ritonavir, etravirine, and rilpivirine in HIV-1-infected pregnant women) listed as a category 3 study in the RMP. The Package Leaflet and the RMP (version 7.0) are updated accordingly. In addition, the

MAH took the opportunity to introduce the latest renewal date in section 9 of the SmPC and the physical address of the Netherlands local representative in the Package Leaflet

13.3.26. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0052/G

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations consisting of: 1) addition to the authorised indications: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, to Xarelto 10 mg. The RMP (version 10) is updated; 2) change in pack sizes of the finished product: change in the number of units in a pack; 3) change in immediate packaging of the finished product: change in type of container or addition of a new container- solid, semi-solid and non-sterile liquid pharmaceutical forms; 4) addition of information on interactions with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) in section 4.5 and a related warning in section 4.4 of the SmPC. In addition, MedDRA[62] terminology is updated in the adverse drug reactions; 5) deletion of 'patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery' and 'remedial pro-coagulant therapy for excessive haemorrhage' from the summary of safety concerns

13.3.27. Roflumilast - DALIRESP (CAP) - EMEA/H/C/002398/X/0031

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

13.3.28. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/X/0035

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

13.3.29. Roflumilast - LIBERTEK (CAP) - EMEA/H/C/002399/X/0032

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension application to add a new strength of 250 µg in a polyvinyl chloride (PVC)/ polyvinylidine chloride (PVDC)/aluminium (Alu) blister of 28 tablets. The RMP (version 18) is updated accordingly

[62] Medical Dictionary for Regulatory Activities

13.3.30. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0009

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams

Scope: Update of section 4.5 of the SmPC to add information on the effect of selexipag administration on the pharmacokinetics of midazolam, its metabolite 1-hydroxymidazolam and the CYP3A4[63] metabolism, based on data from the completed clinical pharmacology study AC-065-114: 'a single-centre, open-label, randomised, two-treatment crossover phase 1 study investigating the effect of selexipag on the pharmacokinetics of midazolam and its metabolite 1-hydroxymidazolam in healthy male subjects'. The RMP (version 5.1) is updated to add the results of study AC-065-114, reclassify 'hyperthyroidism' as an important identified risk and update the PASS timelines and protocol versions in accordance with the current EXPOSURE (PASS AC-065A401m: an observational cohort study of pulmonary arterial hypertension (PAH) patients newly treated with either selexipag or any other PAH-specific therapy, in clinical practice) protocol (version 3) and the EDUCATE (PASS AC-065A403,: an evaluation of risk minimisation measures for medication errors with selexipag during the titration phase in patients with PAH in clinical practice) protocol (version 2)

13.3.31. Siltuximab - SYLVANT (CAP) - EMEA/H/C/003708/II/0023, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report for study CNTO328SMM2001 listed as a category 3 study in the RMP: 'a phase 2, randomised, double-blind, placebo-controlled, multicentre study of siltuximab (anti interleukin-6 (IL-6) monoclonal antibody) in subjects with high-risk smoldering multiple myeloma' to evaluate immunogenicity data. No changes to the product information (PI) are proposed. The RMP (version 23.0) is updated accordingly

13.3.32. Simeprevir - OLYSIO (CAP) - EMEA/H/C/002777/II/0031

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC in order to update the efficacy information following results from study HPC3002, a prospective 3-year follow-up study in subjects previously treated in a phase IIb or phase III study with a TMC435-containing regimen for the treatment of hepatitis C virus (HCV) infection listed as a category 3 study in the RMP and in fulfilment of MEA005. The RMP (version 4.0) is updated accordingly and includes updates of changes already agreed in procedures II/0021, II/0027 and EMEA/H/A-20/1438/C/2777/0019

13.3.33. Sirolimus - RAPAMUNE (CAP) - EMEA/H/C/000273/II/0164

Applicant: Pfizer Limited

[63] Cytochrome P450 3A4

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the treatment of patients with lymphangioleiomyomatosis. As a consequence section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) are updated accordingly. In addition, the MAH took the opportunity to make very minor formatting changes in the Labelling

13.3.34. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0011

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final results from study CLDE225C2301: a phase 2, multicentre, open-label, single-arm study of the efficacy and safety of oral LDE225 in patients with Hegehog (Hh)-signalling pathway activated relapsed medulloblastoma, and study LDE225X2104. a phase 1/2 study of sonidegib (LDE225) in paediatric patients with recurrent or refractory medulloblastoma or other tumours potentially dependent on the Hh-signalling pathway and adult patients with recurrent or refractory medulloblastoma. The RMP (version 6.0) is updated accordingly

13.3.35. 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 randomised 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)

13.3.36. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0019

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.8 of the SmPC of Sivextro concentrate for solution for infusion formulation in order to add information from study BAY119-2631/16121: a phase 3 randomised, double-blind, multicentre study comparing the efficacy and safety of intravenous to oral 6-day tedizolid phosphate and intravenous to oral 10 day linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and change the reported expected frequency of the adverse reaction 'infusion site phlebitis' from 'uncommon' to 'common'. The Package Leaflet is updated accordingly. The RMP (version 3.0) is also updated and includes a proposal to collect safety information regarding tedizolid phosphate by conducting three investigator initiated studies and deleting the original proposed long term safety study. The MAH also took the opportunity to make minor editorial

corrections throughout the product information

13.3.37. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0006

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of section 5.1 of the SmPC based on final results from study 156-08-271 (TEMPO 4:4) listed as a PAES in Annex II. This study is a multicentre, open-label, extension study (extension of trial 156-04-251) to evaluate the long-term efficacy and safety of oral tolvaptan tablet regimens in patients with autosomal dominant polycystic kidney disease (ADPKD) over 5 years. Annex II and the RMP (version 13.1) are updated accordingly to reflect the completion of 156-08-271 study. In addition, the MAH took the opportunity to add the current anatomical therapeutic chemical (ATC) code applicable for tolvaptan as assigned by WHO[64]

13.3.38. Tolvaptan - SAMSCA (CAP) - EMEA/H/C/000980/X/0024

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new strength of 7.5 mg tablets. The RMP (version 13.0) is updated accordingly

14. 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).

14.1. PSUR procedures including centrally authorised products only

14.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201612

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

[64] World Health Organization

14.1.2. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201612

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.3. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201612

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

14.1.4. Daclatasvir - DAKLINZA (CAP) - PSUSA/00010295/201701

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

14.1.5. Efmoroctocog alfa - ELOCTA (CAP) - PSUSA/00010451/201612

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.6. Erlotinib - TARCEVA (CAP) - PSUSA/00001255/201611

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

14.1.7. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201612

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

14.1.8. Human fibrinogen, human thrombin - EVARREST (CAP); EVICEL (CAP); RAPLIXA (CAP); TACHOSIL (CAP) - PSUSA/00010297/201612

Applicant: Omrix Biopharmaceuticals N. V. (Evarrest, Evicel), Mallinckrodt Pharmaceuticals Ireland Limited (Raplixa), Takeda Austria GmbH (TachoSil)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

14.1.9. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201612

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.10. Hydroxocobalamin[65] - CYANOKIT (CAP) - PSUSA/00010228/201611

Applicant: Serb SA

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

14.1.11. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - PSUSA/00001742/201612

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

14.1.12. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201612

Applicant: Grunenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

14.1.13. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/201612

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

14.1.14. Lutropin alfa - LUVERIS (CAP) - PSUSA/00001918/201611

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

[65] Only for products for chemical poisoning

14.1.15. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201612

Applicant: Vericel Denmark ApS, ATMP[66]

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.16. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201612

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

14.1.17. Omalizumab - XOLAIR (CAP) - PSUSA/00002214/201612

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

14.1.18. Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201612

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

14.1.19. Pancreas powder[67] - ENZEPI (CAP) - PSUSA/00010522/201612

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

14.1.20. Pegvisomant - SOMAVERT (CAP) - PSUSA/00002328/201611

Applicant: Pfizer Limited

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

[66] Advanced therapy medicinal product
[67] Centrally authorised product only

14.1.21. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent - SYNFLORIX (CAP) - PSUSA/00009262/201612

Applicant: GSK Biologicals SA

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

14.1.22. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201612

Applicant: Roche Registration Limited

PRAC Rapporteur: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure

14.1.23. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201612

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

14.1.24. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201612

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.25. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201612

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.1.26. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201612

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

14.1.27. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201612

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

14.1.28. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201701

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

14.1.29. Tedizolid phosphate - SIVEXTRO (CAP) - PSUSA/00010369/201612

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

14.1.30. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201612

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

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

14.2.1. Clopidogrel - CLOPIDOGREL ZENTIVA (CAP), ISCOVER (CAP), PLAVIX (CAP); clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP), DUOPLAVIN (CAP); NAP - PSUSA/00000820/201611

Applicant(s): Sanofi-aventis groupe (Clopidogrel Zentiva, Clopidogrel/Acetylsalicylic acid Zentiva, Iscover), Sanofi Clir SNC (DuoPlavin, Plavix), various

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

14.2.2. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201611

Applicant(s): Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

14.3.1. Allergen for diagnostic: skin prick test containing only Phleum pratense[68] - PSUSA/00010466/201610

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

14.3.2. Apomorphine (NAP) - PSUSA/00000227/201611

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

14.3.3. Benzalkonium chloride, chlorhexidine digluconate (NAP) - PSUSA/00010070/201611

Applicant(s): various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

14.3.4. Calcium salts, colecalciferol (NAP) - PSUSA/00010386/201610

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

14.3.5. Chloroquine phosphate, proguanil hydrochloride (NAP) - PSUSA/00010207/201611

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

14.3.6. Clevidipine (NAP) - PSUSA/00010288/201611

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

[68] Product(s) authorised via mutually recognition procedure (MRP) only

14.3.7. Ethinylestradiol, norgestimate (NAP) - PSUSA/00001313/201610

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

14.3.8. Human coagulation factor VII (NAP) - PSUSA/00001619/201610

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

14.3.9. Isoflurane (NAP) - PSUSA/00001786/201610

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

14.3.10. Lacidipine (NAP) - PSUSA/00001815/201610

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

14.3.11. Methoxyflurane (NAP) - PSUSA/00010484/201611

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

14.3.12. Teicoplanin (NAP) - PSUSA/00002878/201611

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

14.3.13. Treprostinil (NAP) - PSUSA/00003013/201611

Applicant(s): various

PRAC Lead: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

14.4. Follow-up to PSUR procedures

14.4.1. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/LEG 104.1

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to LEG 104 [Submission of a cumulative summary table of serious adverse events (SAEs) from clinical trials as requested in the conclusions of EMEA/H/C/PSUSA/00002225/201509 adopted by PRAC in May 2016] as per the request for supplementary information (RSI) adopted in March 2017

15. 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.

15.1. Protocols of PASS imposed in the marketing authorisation(s)[69]

15.1.1. Cidofovir (NAP) - EMEA/H/N/PSP/S/0052.1

Applicant: Emcure Pharma UK Ltd (Cidofovir Emcure Pharma)

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for 'a non-interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use, gather details of adverse events and patient outcome following treatment in a specified indication' as per the conclusion of procedure EMEA/H/N/PSP/S/0052 adopted by PRAC in February 2017

15.1.2. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSA/S/0018

Applicant: Bayer AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Substantial amendment to the previously agreed protocol for an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales (previous conclusions of procedure EMEA/H/C/PSP/0026 adopted by PRAC in June 2015)

[69] In accordance with Article 107n of Directive 2001/83/EC

15.2. Protocols of PASS non-imposed in the marketing authorisation(s)[70]

15.2.1. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 005.1

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Revised PASS protocol in order to collect long-term data using the PsoBest registry, as per the request for supplementary information (RSI) agreed in the conclusions of procedure EMEA/H/C/003746/MEA 005 adopted in September 2015

15.2.2. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/MEA 001

Applicant: Ipsen Pharma

PRAC Rapporteur: Sabine Straus

Scope: PASS protocol for study F-FR-60000-001: a non-interventional prospective study exploring the utilisation of cabozantinib in subjects with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy in real life settings in terms of dose modifications due to adverse events (AEs) when used as a second line therapy or third and later line therapy

15.2.3. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/MEA 003

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Protocol for study 205MS407: a phase 4 observational study in the European Economic Area (EEA) to evaluate the effectiveness of physician hepatic risk management guide as an additional risk minimisation measure in patients prescribed Zinbryta using health insurance claims or patient electronic medical records

15.2.4. Idelalisib - ZYDELIG (CAP) - EMEA/H/C/003843/MEA 016.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: Revised PASS protocol for study GS-EU-313-4226: a cross-sectional PASS to assess healthcare professional (HCP) awareness of risks associated with Zydelig in the European Union (EU) as per the request for supplementary information (RSI) agreed in the conclusion of procedure EMEA/H/C/003843/MEA 016 adopted in March 2017

15.2.5. Levetiracetam - KEPPRA (CAP) - EMEA/H/C/000277/MEA 086

Applicant: UCB Pharma S.A.

[70] 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

PRAC Rapporteur: Laurence de Fays

Scope: Protocol for PASS study EPD172 comparing the incidence of renal failure in patients with epilepsy exposed to levetiracetam or other antiepileptic drugs (final study report: 31 December 2017)

15.2.6. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.4

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Revised protocol for study 178-CL-114: evaluation of cardiovascular events in users of mirabegron and other treatments for overactive bladder as per the request for supplementary information agreed in the conclusions of procedure EMEA/H/C/002388/MEA 001.4 adopted in March 2017

15.2.7. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 009

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Protocol for PASS study 178-PV-002: a drug utilisation study (DUS) of Betmiga (mirabegron) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland

15.2.8. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.10

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Amendment to protocol for study GS-EU-104-0433: a drug utilisation study (DUS) in human immunodeficiency virus (HIV)-1 and hepatitis B virus (HBV) infected paediatric patients to follow-up the effectiveness of the agreed risk minimisation measures, further to the request for supplementary information (RSI) adopted in the conclusions of EMEA/H/C/000419/MEA 256.9 on the second interim report assessment adopted in March 2017

15.3. Results of PASS imposed in the marketing authorisation(s)[71]

None

[71] In accordance with Article 107p-q of Directive 2001/83/EC

15.4. Results of PASS non-imposed in the marketing authorisation(s)[72]

15.4.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/WS1182/0001; Adalimumab - SOLYMBIC (CAP) - EMEA/H/C/004373/WS1182/0001

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report for study 20130258: an open-label, single-arm extension study to evaluate the long-term safety and efficacy of ABP 501 in subjects with moderate to severe rheumatoid arthritis, listed as a category 3 study in the RMP (MEA002). The RMP (version 2.0) is updated accordingly

15.4.2. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0049/G

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped variations consisting of: 1) submission of the final report for a non-interventional PASS study A8081049: a cross-sectional study to evaluate the effectiveness of Xalkori (crizotinib) therapeutic management guide among physicians prescribing Xalkori in Europe. In the light of the study results, the MAH proposed to update Annex II to remove the Xalkori TMG from the educational materials; 2) submission of the final study report for PASS study A8081050, a cross-sectional study to evaluate the effectiveness of Xalkori patient information brochure among non-small cell lung cancer (NSCLC) patients receiving Xalkori treatment in Europe. The MAH also took the opportunity to state 'monotherapy' in section 4.1 of the SmPC as requested by the CHMP and to bring the product information (PI) in line with the latest QRD template

15.4.3. Epoetin zeta - RETACRIT (CAP) - EMEA/H/C/000872/II/0077

Applicant: Hospira UK Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Submission of the final report from the registry based healthcare database study HDBS study linked to PASCO (PMS-830-07-0043: a post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia) listed as a category 3 study in the RMP. This is an observational study on the incidence of thromboembolic events in patients with renal anaemia treated with erythropoietin zeta as compared with erythropoietin alfa and other erythropoiesis-stimulating agents (ESA)

15.4.4. Epoetin zeta - SILAPO (CAP) - EMEA/H/C/000760/II/0045

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Valerie Strassmann

[72] 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

Scope: Submission of the final report from the registry based healthcare database study HDBS study linked to PASCO (PMS-830-07-0043: a post-authorisation safety cohort observation of Silapo (epoetin zeta) for the treatment of renal anaemia) listed as a category 3 study in the RMP. This is an observational study on the incidence of thromboembolic events in patients with renal anaemia treated with erythropoietin zeta as compared with erythropoietin alfa and other erythropoiesis-stimulating agents (ESA). The RMP (version 11) is updated accordingly

15.4.5. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1188/0157; LIPROLOG (CAP) - EMEA/H/C/000393/WS1188/0120

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final report for a non-interventional PASS EUPAS 13422 aiming at evaluating the impact of additional risk minimisation measures on healthcare professionals and on patients' understanding and their behaviour regarding the risk of hypoglycaemia and/or hyperglycaemia due to medication errors associated with administration of Humalog 200 U/mL KwikPen or Liprolog 200 U/mL KwikPen

15.4.6. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0095, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final results of the non-interventional, observational category 3 PASS study CC-5013-PASS-001 in subjects treated with lenalidomide to further characterise the safety profile of lenalidomide plus dexamethasone in the treatment of relapsed and/or refractory (R/R) multiple myeloma (MM) in a real-world setting

15.4.7. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0101

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report (CSR) for TYGRIS: a post-marketing safety observational cohort programme designed to obtain long-term safety data (approximately 5 years) in subjects with multiple sclerosis (MS) treated with natalizumab, and comprising parallel studies 101MS402 (United States and Canada) and 101MS403 (rest of the World). The RMP (version 23) is updated accordingly

15.4.8. Rufinamide - INOVELON (CAP) - EMEA/H/C/000660/II/0041, Orphan

Applicant: Eisai Ltd

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final clinical study report (CSR) for study E2080-E044-401: a European registry of anti-epileptic drug use in patients with Lennox-Gastaut syndrome (LGS), listed as a category 3 study in the RMP, in fulfilment of MEA 002.1. E2080-E044-401

is a non-interventional EU registry study entering patients (aged ≥4 years) with LGS who required a modification in anti-epileptic therapy (either the addition of another anti-epileptic drugs (AED) or the change of one drug to another) in order to evaluate the long-term safety of rufinamide

15.4.9. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0069

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final 5-year report from study (ZOL446H2422) listed as a category 3 study in the RMP: a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta against oral bisphosphonates and untreated population controls

15.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[73]

15.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 053.4

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to MEA 053.3: revised first interim study report [epidemiology PASS study report for study ALGMYC07390 evaluating the prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions] as per the request for supplementary information (RSI) adopted by PRAC in March 2017

15.5.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.2

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Two-yearly interim report on study PTC124-GD-025o-DMD: a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting (RMP category 3 study) (three year interim report due on 30 April 2018)

15.5.3. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Second interim results (semi-annual report) for a category 3 study TMC207TBC4002: a multinational prospective multidrug resistant tuberculosis (MDRTB) patient registry to monitor bedaquiline safety, utilisation, and emergence of resistance (final

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

study report: Q2 2020)

15.5.4. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002614/MEA 013

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual report (integrated safety analysis report) for clinical studies: 1) BRF113683 (BREAK-3): a two-arm, open-label, randomised Phase III pivotal study comparing oral dabrafenib with intravenous dacarbazine (DTIC), 2) MEK115306 (COMBI-d): a two-arm, double-blinded, randomised, Phase III study comparing dabrafenib and trametinib combination therapy (to be referred to as combination therapy in this report) with dabrafenib administered with a trametinib placebo (dabrafenib monotherapy) and 3) MEK116513 (COMBI-v): a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma on secondary malignancies in patients treated with dabrafenib in randomised controlled trials to comply with the additional pharmacovigilance activity as requested in the RMP. The report identifies and characterises the risk of treatment-emergent cutaneous and non-cutaneous malignancies in randomised controlled clinical trials of dabrafenib; alone or in combination with other anticancer drugs

15.5.5. Degarelix - FIRMAGON (CAP) - EMEA/H/C/000986/MEA 013.2

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Sixth annual progress report (data cut-off date: 18 February 2017) for PASS FE 200486 CS39: a prospective observational safety study in patients with advanced prostate cancer treated with Firmagon (degarelix) or a gonadotropin-releasing hormone (GnRH) agonist

15.5.6. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.2

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Third annual study report (reporting period: 14 February 2016 to 13 February 2017) for the multicentre, multinational, observational Morquio A registry study (MARS): a voluntary observational registry study to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population and to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa) (final clinical study report (CSR): March 2025)

15.5.7. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 023

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: First progress report of Bexsero pregnancy registry: an observational study of the safety of Bexsero exposure in pregnant women and their offspring

15.5.8. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.11

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response [second interim study report for a drug utilisation study (DUS) GS-EU-104-0433 in paediatric patients with human immunodeficiency virus (HIV)-1 infection, to describe the characteristics of HIV-1 infected patients up to 18 years of age treated with Viread within the EU in order to determine if they are being managed in accordance with the European SmPC] to the request for supplementary information (RSI) adopted in the conclusions of EMEA/H/C/000419/MEA 256.9 in March 2017

15.6. Others

15.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.7

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Bi-annual status reports for study DNE3001/CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (IDMC report dated March 2017)

15.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.7

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status reports for study DNE3001/CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (IDMC report dated March 2017)

15.6.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/LEG 058.1

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to LEG 058 [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 by CHMP in

December 2016

15.6.4. Telavancin - VIBATIV (CAP) - EMEA/H/C/001240/ANX 007.5

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Submission of a pregnancy exposure follow-up questionnaire in the context of the pregnancy exposure registry (9809-CL-1409), as per the request for supplementary information (RSI) adopted in the conclusions of procedure EMEA/H/C/001240/ANX 007.4 adopted in September 2016

15.6.5. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/LEG 031

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: Review on causality assessment and analysis of hypotension cases

15.7. New Scientific Advice

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

15.8. Ongoing Scientific Advice

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

15.9. 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.

16. 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.

16.1. Annual reassessments of the marketing authorisation

16.1.1. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0070 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

16.2. Conditional renewals of the marketing authorisation

16.2.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/R/0013 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the of the marketing authorisation

16.2.2. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0051 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

16.2.3. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0003 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

16.2.4. Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/R/0004 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

16.2.5. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0005 (without RMP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

16.3. Renewals of the marketing authorisation

16.3.1. Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/R/0037 (without RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

16.3.2. Florbetapir (^{18}F) - AMYVID (CAP) - EMEA/H/C/002422/R/0026 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

16.3.3. Ibandronic acid - IBANDRONIC ACID ACCORD (CAP) - EMEA/H/C/002638/R/0013 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

16.3.4. Imatinib - IMATINIB TEVA (CAP) - EMEA/H/C/002585/R/0028 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

16.3.5. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/R/0027 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

16.3.6. Insulin degludec, insulin aspart - RYZODEG (CAP) - EMEA/H/C/002499/R/0024 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

16.3.7. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/R/0023 (with RMP)

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

16.3.8. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/R/0053 (without RMP)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

16.3.9. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/R/0026 (with RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

17. Annex I - Product related pharmacovigilance inspections

17.1. List of planned pharmacovigilance inspections

None

17.2. 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 minutes.

17.3. Others

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 minutes.

18. Annex I - Other safety issues for discussion requested by the CHMP or the EMA

18.1. Safety related variations of the marketing authorisation

None

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

None

18.3. Other requests

None

18.4. Scientific advice

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

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 3-6 July 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	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- via telephone*	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
			declared	
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No restrictions applicable to this meeting	Full involvement
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
Sofia Trantza	Alternate	Greece	No restrictions applicable to this meeting	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
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
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	3.4.1. Gadolinium-containing contrast agents (GdCA) 3.4.1. Factor VIII 4.2.1 Desloratadine, loratadine 4.3.2 Ciprofloxacin, meropenem 7.1.3 Levonorgestrel 11.1.3 Levonorgestrel
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	3.2.2. Paracetamol 4.2.1 Desloratadine, loratadine 4.3.1 Amoxicillin 4.3.2 Ciprofloxacin, meropenem
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
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
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
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Hugues Malonne	Expert - in person*	Belgium	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
			this meeting	
Flora Musuamba Tshinanu	Expert - via telephone*	Belgium	No interests declared	Full involvement
Adriana Andrić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Sanja Prpić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Maja Tabak Slošić	Expert - via telephone*	Croatia	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Outi Maki-Ikola	Expert - in person*	Finland	No restrictions applicable to this meeting	Full involvement
Päivi Ruokoniemi	Expert - via telephone*	Finland	No interests declared	Full involvement
Alban Dhanani	Expert - via telephone*	France	No interests declared	Full involvement
Nathalie Dumarcet	Expert - via telephone*	France	No interests declared	Full involvement
Marc Martin	Expert - via telephone*	France	No interests declared	Full involvement
Peter Bachmann	Expert - in person*	Germany	No interests declared	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Anke Blumberg	Expert - via telephone*	Germany	No interests declared	Full involvement
Annette Hinze	Expert - via telephone*	Germany	No interests declared	Full involvement
Tobias Lamkemeyer	Expert - in person*	Germany	No interests declared	Full involvement
Kerstin Löschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Walburga Lütkehermölle	Expert - via telephone*	Germany	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda / minutes for which restrictions apply
Peter Mayer	Expert - via telephone*	Germany	No interests declared	Full involvement
Johannes Pohly	Expert - via telephone*	Germany	No interests declared	Full involvement
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Dörte Schwabe	Expert - via telephone*	Germany	No interests declared	Full involvement
Massimiliano Sarra	Expert - via telephone*	Italy	No interests declared	Full involvement
Liana Gross	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Christel Hoeve	Expert - in person*	Netherlands	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Sílvia Duarte	Expert - in person*	Portugal	No interests declared	Full involvement
Mário Miguel Rosa	Expert - in person*	Portugal	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Ulf Olsson	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Tomas Salmonson	Expert - in person*	Sweden	No interests declared	Full involvement
Nigel Hoggard	Expert - via telephone*	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/ema/