9 June 2017
EMA/PRAC/419638/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 2-5 May 2017

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 2-5 May 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 Chairperson announced that Helga Haugom Olsen was to step down as PRAC member for Norway after the current PRAC plenary meeting. In addition, the PRAC noted that Claire Ferard was attending her last meeting as PRAC member for France. The PRAC thanked Helga Haugom Olsen and Claire Ferard for their contribution to the work of the Committee.

1.2. Agenda of the meeting on 2-5 May 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 3-6 April 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 3-6 April 2017 were published on the EMA website on 2 June 2017 (EMA/PRAC/271304/2017).

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

2.4. Planned public hearings

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. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant(s): Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Ana Sofia Diniz Martins; PRAC Co-rapporteur: Julie Williams

Scope: Review of the benefit-risk balance following notification by the United Kingdom 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 retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[1] to evaluate measures currently in place for pregnancy prevention and the possible risk of neuropsychiatric disorders for oral and topical retinoids. For further background, see PRAC minutes July 2016, PRAC minutes September 2016, PRAC minutes October 2016, PRAC minutes December 2016, PRAC minutes January 2017 and PRAC minutes March 2017.

Summary of recommendation(s)/conclusions

[1] Tretinoin may also be used to treat promyelocytic leukaemia

The PRAC discussed the joint assessment report prepared by the Rapporteurs and adopted a second list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/461927/2016 Rev 2).

3.3. Procedures for finalisation

3.3.1. 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: Julie Williams; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is to be concluded for the review of factor VIII-containing medicines indicated for the treatment of haemophilia A that assessed the impact of the results of the SIPPET study by *Peyvandi et al*.[2] on the benefit risk of factor-VIII containing medicines and considered the need for any potential for risk minimisation measures or other changes to the marketing authorisations of these medicinal products. A final assessment of the data was produced by the Rapporteurs according to the agreed timetable. For further background, see PRAC minutes July 2016, PRAC minutes November 2016, PRAC minutes January 2017, PRAC minutes February 2017 and PRAC minutes March 2017.

Discussion

The PRAC reviewed the totality of the submitted data with regard to the risk of inhibitor development for the classes of recombinant and plasma derived factor VIII-containing medicines in previously untreated patients (PUPs). This included the findings of the SIPPET study together with the presentation made by its authors at the February 2017 meeting, data generated in individual clinical trials and a range of observational studies submitted by the MAHs, including data generated in large multicentre cohort studies, as well as data submitted by the EU NCAs. In addition, the PRAC took into account the views expressed by the ad-hoc expert group meeting and discussed the conclusions reached by the Rapporteurs. Finally, two oral explanations took place at the current meeting.

[2] Peyvandi F. et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Eng J Med. 2016 May 26;374(21):2054-64) (SIPPET study)

The PRAC noted that the SIPPET study was not designed to evaluate the risk of inhibitor development for individual medicines, and included a limited number of factor VIII-containing products in total. Indeed, due to the heterogeneity across medicinal products, there exist uncertainties in extrapolating the findings of studies evaluating only class effects to individual products, particularly to the products that are not included in such studies.

The PRAC also considered that studies conducted to date suffer from a variety of methodological limitations and, on balance, there was no clear and consistent evidence to suggest differences in relative risks between factor VIII product classes based on available data. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAHs' responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between recombinant factor VIII and plasma derived-factor VIII product classes. Given these are heterogeneous medicinal products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies. The PRAC noted that the efficacy and safety of factor VIII products as indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A have been established.

Overall, the PRAC considered that product information updates for factor VIII-medicinal products were warranted to include a warning on the clinical importance of monitoring patients for factor VIII inhibitor development and to reflect that all human factor VIII-containing medicinal products carry a risk of inhibitor development, within a frequency of 'very common' and 'uncommon', for PUPs and previously treated patients (PTPs) respectively, unless justified by product specific data.

Summary of recommendation(s)/conclusions

The PRAC concluded that the benefit-risk balance of the human plasma derived and recombinant coagulation factor VIII-containing medicinal products remains favourable. The PRAC adopted a recommendation to vary the terms of the marketing authorisations[3] for human plasma derived factor VIII- and recombinant coagulation factor VIII-containing medicinal products and adopted a recommendation to be considered by the CHMP for an opinion.

See EMA Press Release (EMA/153837/2017) entitled 'PRAC concludes there is no clear and consistent evidence of a difference in inhibitor development between classes of factor VIII medicines'.

3.4. Re-examination procedures[4]

3.4.1. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - 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

[3] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly
[4] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

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 and PRAC minutes April 2017.

Upon receipt of the grounds for re-examination from some of the MAHs concerned by this referral procedure, the PRAC will initiate a re-examination procedure, expected to conclude in July 2017.

Summary of recommendation(s)/conclusions

The PRAC confirmed the need to consult an ad-hoc expert group provisionally scheduled on 19 June 2017, and discussed a preliminary list of experts (LoE).

Post-meeting note: Following receipt of the grounds for re-examination, the PRAC adopted by written procedure on 17 May 2017 a revised timetable for conducting the review concluding in July 2017 (EMA/PRAC/195601/2016 Rev.7).

3.5. Others

None

4. Signals assessment and prioritisation[5]

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. Insulin[6]: insulin aspart – NOVOMIX (CAP), NOVORAPID (CAP); insulin bovine (NAP); insulin degludec – TRESIBA (CAP); insulin degludec, insulin aspart – RYZODEG (CAP), insulin degludec, liraglutide – XULTOPHY (CAP); insulin detemir – LEVEMIR (CAP); insulin glargine – ABASAGLAR (CAP), LANTUS (CAP), LUSDUNA (CAP), TOUJEO

[5] 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

(CAP); insulin glulisine – APIDRA (CAP); insulin human (rDNA) – ACTRAPHANE (CAP), ACTRAPID (CAP), INSULATARD (CAP), INSULIN HUMAN WINTHROP (CAP), INSUMAN (CAP), MIXTARD (CAP), PROTAPHANE (CAP); insulin human, insulin isophane (NAP); insulin lispro – HUMALOG (CAP), LIPROLOG (CAP); insulin porcine (NAP)

Applicant(s): Eli Lilly Regional Operations GmbH (Abasaglar); Eli Lilly Nederland B.V. (Humalog, Liprolog); Novo Nordisk A/S (Actraphane, Actrapid, Insulatard, Levemir, Mixtard, NovoMix, NovoRapid, Protaphane, Ryzodeg, Tresiba, Xultophy); Merck Sharp & Dohme Limited (Lusduna); Sanofi-aventis Deutschland GmbH (Apidra, Lantus, Toujeo, Insulin Human Winthrop, Insuman); various

PRAC Rapporteur: Julie Williams

Scope: Signal of potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia

EPITT 18893 – New signal

Lead Member State(s): BE, DK, IT, NL, SE, UK

Background

Insulin is a peptide hormone produced by beta cells of the pancreatic islets. As medicinal products, insulin[7] and insulin analogues[8] are indicated for the treatment of diabetes under various conditions.

After the publication in November 2016 of a UK National Health Service (NHS) patient safety alert about the risk of withdrawing insulin from pen devices or reusable cartridges, UK healthcare professionals alerted the Medicines and Healthcare Products Regulatory Agency (MHRA) that the product information of some insulin-containing medicines includes explicit wording allowing the practice of extraction of insulin from pre-filled pens or cartridges using a syringe. This may increase the risk of medication errors and lead to dysglycaemia. UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the reports of incidents associated with extraction of insulin from pens and cartridges using a syringe. Having considered the available evidence and taking into account the current 'EMA guidance on risk minimisation strategy for high-strength and fixed-combination insulin products' (EMA/686009/2014), the PRAC agreed that it would be useful to update the product information with respect to this issue.

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for high strength and fixed combination of insulin-containing products should submit to EMA, within 60 days, a variation for amending the product information[9] to ensure that wording on medication errors related to insulin extraction from a pre-filled pen using a syringe is aligned with the current 'EMA guidance on risk minimisation for high strength and fixed combination insulin-containing products'.

[6] Pre-filled pens and cartridges
[7] Insulin of animal origin
[8] Recombinant insulin, including human insulin
[9] Update of SmPC sections 4.2, 4.4 or 6.6. The package leaflet is to be updated accordingly

- The MAHs of standard (100 units/mL) and lower (<100 units/mL) strength insulin-containing products that include in their product information the possibility of withdrawing insulin from cartridges with a syringe should submit to EMA by 26 July 2017 a justification for having such a wording taking into account the risk of potential medication error and possible contamination that may occur as a result of such a practice.
- Finally, the PRAC concurred that the views of healthcare professional (HCP) experts on medication error and diabetes should be sought in due course on the issues surrounding extraction of insulin from pre-filled pens/cartridges/pumps for further discussion at PRAC on the appropriate product information wording.

For the full PRAC recommendation, see EMA/PRAC/252869/2017 published on 29/05/2017 on the EMA website.

4.3. Signals follow-up and prioritisation

4.3.1. Amoxicillin (NAP)

Applicant(s): various

PRAC Rapporteur: Jan Neuhauser

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

EPITT 18802 – Follow-up to January 2017

Background

The MAH 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. For background information, see PRAC minutes January 2017.

Discussion

Having considered the evidence from the cumulative review of all cases of DRESS syndrome associated with amoxicillin-containing products as provided by the MAH, and the available evidence from case reports in EudraVigilance and in the literature, the PRAC agreed that the MAH of Amoxil (amoxicillin) should provide additional detailed information concerning cases of DRESS syndrome associated with amoxicillin-containing products, together with a discussion on the risk of protopathic bias that might occur when amoxicillin/amoxicillin clavulanate is inadvertently prescribed for an early manifestation of DRESS syndrome not yet correctly diagnosed. In addition, full consideration should be given to amoxicillin-induced flare in patients with DRESS induced by other drugs and/or human herpes virus 6 (HHV6). The MAH should also discuss the need to amend the product information, PSUR and RMP accordingly, as necessary.

Summary of recommendation(s)

- The MAH for Amoxil (amoxicillin) should submit to EMA, within 30 days, a detailed review of the signal of DRESS syndrome together with a discussion on the risk of protopathic bias. The MAH should further evaluate available literature and information on amoxicillin-induced flare in patients with DRESS induced by other drugs and/or

HHV6. The MAH should include a proposal for amending the product information, PSUR and RMP as appropriate.

- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.2. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/SDA/027

Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Signal of cytomegalovirus (CMV) reactivation

EPITT 18789 – Follow-up to December 2016

Background

The MAH replied to the request for information on the signal of cytomegalovirus (CMV) reactivation and the responses were assessed by the Rapporteur. For background information, see PRAC minutes December 2016.

Discussion

Having considered the available evidence in EudraVigilance, clinical trials and in the literature, and the known association of brentuximab vedotin with infections, the PRAC recommended the addition of a warning on CMV (reactivation) to the product information of brentuximab vedotin-containing medicinal product(s) to ensure that patients are carefully monitored during brentuximab vedotin treatment for the emergence of this serious and opportunistic infection. In addition, CMV infection or reactivation should be added as an undesirable effect with an uncommon frequency.

Summary of recommendation(s)

- The MAH for brentuximab vedotin-containing medicinal products should submit to EMA, within 60 days, a variation to amend the product information[10].

For the full PRAC recommendation, see EMA/PRAC/252869/2017 published on 29/05/2017 on the EMA website.

4.3.3. Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/SDA/014

Applicant(s): Roche Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Signal of colitis

EPITT 18793 – Follow-up to December 2016

Background

The MAH replied to the request for information on the signal of colitis and the responses were assessed by the Rapporteur. For background information, see PRAC minutes December 2016.

Discussion

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

Having considered the available evidence from the cumulative review provided by the MAH, the PRAC did not consider that there was sufficient evidence to support a causal relationship between treatment with pirfenidone and colitis. Therefore, the PRAC concurred that there was no need to introduce any changes to the product information at this stage. The MAH should continue to monitor all sources of information under MedDRA HLT[11] colitis (excluding infective) and should provide specific updates on these events in future PSURs.

Summary of recommendation(s)

- The MAH for Esbriet (pirfenidone) should continue to monitor all sources of information under the HLT term colitis (excluding infective) and should provide specific updates on these events in future PSURs.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the CHMP on the proposed RMPs for a number of medicinal products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights).

See also Annex I 15.1.

5.1.1. Beclometasone dipropionate anhydrous, formoterol fumarate dihydrate, glycopyrronium bromide - EMEA/H/C/004257

Scope: Treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) with airflow limitation and who are at risk of exacerbations

5.1.2. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - EMEA/H/C/004391

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

5.1.3. Lutetium (^{177}Lu) dotatate - EMEA/H/C/004123, Orphan

Applicant: Advanced Accelerator Applications

Scope: Treatment of gastro-entero-pancreatic neuroendocrine tumours

For previous reference, see PRAC minutes September 2016.

5.1.4. Paclitaxel - EMEA/H/C/004154, Orphan

Applicant: Oasmia Pharmaceutical AB

[11] Medical dictionary for regulatory activities – High level term

Scope: Treatment of ovarian cancer

5.1.5. Trastuzumab - EMEA/H/C/004346

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

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0085

Applicant: GSK Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of study EPI-HPV-069: a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The RMP (version 18) is updated accordingly and includes minor updates related to other studies

Background

Human papillomavirus (HPV) vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18, indicated for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic HPV types.

The CHMP is evaluating a type II variation for Cervarix, a centrally authorised HPV vaccine, evaluating a meta-analysis assessing the risk of three autoimmune diseases following vaccination with Cervarix: autoimmune thyroiditis (AIT), Guillain-Barre syndrome (GBS) and inflammatory bowel disease (IBD). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes December 2016.

Summary of advice

- The RMP version 19 for Cervarix (HPV vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)) in the context of the variation under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC advised that the MAH should be requested to perform a feasibility assessment for a study investigating the potential association between Cervarix and AIT. The feasibility assessment should address the study design and analytical approach (self-

control case series and case-control methods), study endpoints, potential data sources and several methodological issues (e.g. case definition, case identification, time-to-onset, risk period, environmental factors). The RMP should be updated accordingly.

5.3.2. Liraglutide - VICTOZA (CAP) - EMEA/H/C/001026/II/0042

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the prevention of major adverse cardiovascular events (MACE) in adults with type 2 diabetes mellitus (T2DM) at high cardiovascular risk and as an adjunct to standard of care therapy in section 4.1 of the SmPC implementing the clinical study results of the LEADER study (EX2211-3748): liraglutide effect on and action in diabetes, evaluation of cardiovascular outcome results (category 3 study: to specifically address the important potential risk of cardiovascular disorders in patients with T2DM). As a consequence, sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC, the Package Leaflet, Labelling and RMP (version 27) are updated accordingly

Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue indicated for the treatment of adults with type 2 diabetes mellitus (T2DM) to achieve glycaemic control, as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications, as well as in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating an extension of the therapeutic indication for Victoza, a centrally authorised product containing liraglutide, to include the prevention of major adverse cardiovascular events (MACE) in adults with T2DM at high cardiovascular risk and as an adjunct to standard of care therapy based on the results of the LEADER study[12]. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of the therapeutic indication. For further background, see PRAC minutes February 2017.

Summary of advice

- The RMP version 27.1 for Victoza (liraglutide) in the context of the extension of indication application under evaluation by the CHMP could be considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC agreed that 'neoplasms (including melanoma)' and 'pancreatic cancer' should remain in the RMP as important potential risks. In addition, the MAH should clarify whether four non-confirmed events assessed by an expert as 'pancreatic carcinoma (metastatic)' were included in the analyses on pancreatic neoplasms in the LEADER study.

[12] Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results to specifically address the important potential risk of cardiovascular disorders in patients with type 2 diabetes mellitus

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. Alglucosidase alfa - MYOZYME (CAP) - PSUSA/00000086/201609

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Alglucosidase alfa is an enzyme indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Myozyme, a centrally authorised medicine containing alglucosidase alfa, 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 risk-benefit balance of Myozyme (alglucosidase alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'infusion site swelling', 'infusion site induration' and 'infusion site extravasation' as undesirable effects with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should provide detailed analyses of available data from the lactation sub-registry[14] and the safety sub-registry[15] of the Pompe registry[16].

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. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/201610 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

[13] 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
[14] Sub-registry to determine the presence of alglucosidase alfa in breast milk from women with Pompe disease treated with alglucosidase alfa (observational, prospective)
[15] Prospective safety sub-registry to assess anaphylaxis and severe allergic reactions, and severe cutaneous and systemic immune complex mediated reactions with alglucosidase alfa treatment
[16] Global observational database. The registry provides a repository that allows for the exchange of information and aggregate data to facilitate clinical decision-making and data reports, and serves as a vehicle for collaborative studies

Scope: Evaluation of a PSUSA procedure

Background

Dapagliflozin is a selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control both as monotherapy and as add-on combination therapy, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Edistride and Forxiga, centrally authorised medicines containing dapagliflozin, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Edistride and Forxiga (dapagliflozin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on diabetic ketoacidosis (DKA) and include the occurrence of fatal cases. Therefore, the current terms of the marketing authorisation(s) should be varied[17].

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. Edoxaban - LIXIANA (CAP) - PSUSA/00010387/201610

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Edoxaban is a direct and reversible inhibitor of factor Xa indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) under certain conditions, and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lixiana, a centrally authorised medicine containing edoxaban, 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 risk-benefit balance of Lixiana (edoxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'headache', 'abdominal pain' and 'dizziness' as undesirable effects with a common frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

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

- In the next PSUR, the MAH should provide a detailed review of all relevant data relating to hepatobiliary disorder including that from clinical trials, serious and non-serious post-marketing cases and the published literature. The MAH review should also include a discussion on possible mechanisms and patterns of hepatocellular injury. Furthermore, the MAH should provide further information relating to the cases of drug-induced liver injury (DILI) and ascites.

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. Eltrombopag - REVOLADE (CAP) - PSUSA/00001205/201609

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Eltrombopag is a thrombopoietin receptor agonist indicated for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP), as well as in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia and in adult patients with acquired severe aplastic anaemia, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revolade, a centrally authorised medicine containing eltrombopag, 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 risk-benefit balance of Revolade (eltrombopag) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the imposition of educational material as an additional risk minimisation measure for hepatotoxicity, thromboembolic events and potential for off-label use, as this information is already included in the currently approved product information, so the initial objectives to increase the awareness of the healthcare providers and patients on the relevant safety concerns are met. Therefore, the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should further justify the reason not to include 'retinal haemorrhage' in the product information. In addition, the MAH should review the list of safety concerns of the RMP in order to remove the important identified risk of interaction with antacid, mineral supplements, dairy products (polyvalent cations) as well as missing information such as use in pregnant and lactating women, off-label use and several patient sub-populations with hepatitis C virus. Finally, the MAH should provide a review of adverse drug reactions (ADR) cases reported during pregnancy.

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

6.1.5. Empagliflozin – JARDIANCE (CAP); empagliflozin, metformin - SYNJARDY (CAP) - PSUSA/00010388/201610

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) indicated alone or in combination with metformin, a biguanide, for the treatment of type 2 diabetes in adults aged 18 years old and older under certain conditions.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise an existing warning on diabetic ketoacidosis (DKA) to include the occurrence of fatal cases, as well as 'angioedema' as an undesirable effect with an unknown frequency, 'rash' with a common frequency and 'urticaria' with an uncommon frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAH should provide a detailed review of cases of 'acute renal failure'. In addition, the MAH should state how many cases presented with an atypical presentation of DKA and for which indications these patients were on treatment with empagliflozin, and provide the number of post-marketing case reports including predisposing factors to ketoacidosis. Furthermore, the MAH should present a cumulative review of complicated urinary tract infections (UTIs) for both clinical trials and post-marketing data and propose product information updates if deemed appropriate. Finally, the MAH should provide further details on any serious adverse reactions reported regarding the risk of liver injury, as well as provide the outcome of the pregnancy cases following empagliflozin exposure.

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

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

6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.6. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201609 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Insulin degludec is a basal insulin and liraglutide a glucagon-like peptide-1 (GLP-1). In combination, insulin degludec/liraglutide is indicated for the treatment of type 2 diabetes mellitus (T2DM) in adults to improve glycaemic control under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xultophy, a centrally authorised medicine containing insulin degludec/liraglutide, 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 risk-benefit balance of Xultophy (insulin degludec/liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'cholelithiasis' and 'cholecystitis' as undesirable effects with an uncommon frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should closely monitor cases of 'blood glucose increased' or 'hyperglycaemia'.

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. Lurasidone - LATUDA (CAP) - PSUSA/00010114/201610

Applicant: Sunovion Pharmaceuticals Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Lurasidone is a selective blocking agent of dopamine and monoamine effects indicated for the treatment of schizophrenia in adults aged 18 years and over.

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

[21] 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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Latuda (lurasidone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hyponatremia' as an undesirable effect with an uncommon frequency. In addition, the frequency of the undesirable effects 'hypersensitivity', 'rash' and 'pruritus' should be changed from unknown to uncommon, as well as changing the frequency of 'angioedema' from unknown to rare. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should provide detailed reviews of 'thromboembolic events' and 'urinary retention'.

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

6.1.8. Nintedanib[23] - OFEV (CAP) - PSUSA/00010319/201610

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

Background

Nintedanib is a tyrosine kinase inhibitor (TKI) indicated[24] in adults for the treatment of idiopathic pulmonary fibrosis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Ofev (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current warning on diarrhoea to state that it can lead to dehydration and electrolyte disturbances and to add 'dehydration' as an undesirable effect with an uncommon frequency. In addition, the current warning on haemorrhage should be also amended to reflect that non-serious and serious bleeding events have been reported in the post-marketing period (including patients with or without anticoagulant therapy or other drugs that could cause bleeding), as well as the current warning on gastrointestinal perforation to state in particular that

[22] 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
[23] Respiratory indication only
[24] Nintedanib is also indicated in other indication(s) as part of separate marketing authorisation(s)

cases of gastrointestinal perforation have been reported in post-marketing settings. Therefore, the current terms of the marketing authorisation(s) should be varied[25].

- In the next PSUR, the MAH should provide a cumulative analysis of cases reporting off-label use of nintedanib in doses below the initial recommended dose with a focus on differences in the safety profile and in efficacy. In addition, the MAH should provide a further detailed analysis of cases reporting suicide, suicidal ideation and depression with reported positive dechallenge and/or rechallenge. Furthermore, the MAH should provide a cumulative analysis of cases reporting (acute) renal failure and 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.

6.1.9. Talimogene laherparepvec - IMLYGIC (CAP) - PSUSA/00010459/201610

Applicant: Amgen Europe B.V., ATMP[26]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Talimogene laherparepvec is an oncolytic immunotherapy indicated for the treatment of adults with unresectable melanoma under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imlygic, a centrally authorised medicine containing talimogene laherparepvec, 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 risk-benefit balance of Imlygic (talimogene laherparepvec) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should keep under scrutiny the causality of cardiac events reported with Imlygic. Moreover, the MAH should discuss the addition of the undesirable effect 'local bleeding' to the product information with an unknown frequency.

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. Thalidomide - THALIDOMIDE CELGENE (CAP) - PSUSA/00002919/201610

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

[25] Update of SmPC section 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
[26] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

Background

Thalidomide is an immunosuppressant with anti-inflammatory and potential anti-neoplastic activities indicated in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged 65 years or more, or ineligible for high dose chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Thalidomide Celgene, a centrally authorised medicine containing thalidomide, 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 risk-benefit balance of Thalidomide Celgene (thalidomide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should discuss any new cases of bradycardia reported with both thalidomide and bortezomib, discuss any potential interaction between both treatments and propose product information updates if deemed appropriate. In addition, the MAH should provide a detailed review of cases of Sweet's syndrome.
- The PRAC concluded that there is a high degree of compliance with the pregnancy prevention programme (PPP) and that the data do not suggest that off-label use is associated with reduced compliance with the PPP. The MAH should ensure that the PPP continues to be implemented in each EU Member State as per the 'conditions or restrictions with regard to the safe and effective use of the medicinal product' (Annex II-D).

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 - INCRUSE (CAP) - PSUSA/00010263/201610

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Umeclidinium bromide is a long acting muscarinic receptor antagonist 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 Incruse, a centrally authorised medicine containing umeclidinium bromide, 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 risk-benefit balance of Incruse (umeclidinium bromide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'intraocular pressure increased' 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 closely monitor cases of 'eye pain', 'angle closure glaucoma' and 'bladder outlet obstruction' as well as monitor cases of overdose/medication errors reported with umeclidinium bromide, hypersensitivity reactions and off label use.

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

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

See also Annex I 16.2.

6.2.1. Mercaptopurine - XALUPRINE (CAP); NAP - PSUSA/00001988/201609

Applicant: Nova Laboratories Limited (Xaluprine), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Mercaptopurine is an antineoplastic agent indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Xaluprine, a centrally authorised medicine containing mercaptopurine, and nationally authorised medicines containing mercaptopurine, 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 risk-benefit balance of mercaptopurine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the increased risk of severe toxicity in patients with inherited mutated NUDT15 gene treated with 6-mercaptopurine as these patients may require dose reduction, particularly those being NUDT15 variant homozygotes. Genotypic testing of NUDT15 variants may be considered before initiating 6-mercaptopurine therapy and in any event, close monitoring of blood counts is necessary. In addition, a warning should be added on the increased risk of infections (viral, fungal bacterial infections and viral reactivation) in

[27] 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

order to ensure that prior exposure to or infection with varicella zoster virus is taken into consideration prior to starting treatment. Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Furthermore, 'bacterial and viral infections' and 'infections associated with neutropenia' should also be added as undesirable effects with an uncommon frequency. Therefore, the current terms of the marketing authorisations should be varied[28].

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.

6.2.2. Octocog alfa - ADVATE (CAP); HELIXATE NEXGEN (CAP); IBLIAS (CAP); KOGENATE BAYER (CAP); KOVALTRY (CAP); NAP - PSUSA/00002200/201608

Applicants: Baxter AG (Advate), Bayer Pharma AG (Helixate NexGen, Iblias, Kogenate, Bayer, Kovaltry), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Octocog alfa is a recombinant human antihaemophilic factor VIII (fVIII) indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Advate, Helixate NexGen, Iblias, Kogenate Bayer and Kovaltry, centrally authorised medicines containing octocog alfa, and nationally authorised medicines containing octocog alfa, 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 risk-benefit balance of octocog alfa-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained. This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 31 of Directive 2001/83/EC for factor VIII-containing products (EMEA/H/A-31/1448). See under 3.3.1.

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.

[28] 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

6.3.1. Cetirizine, pseudoephedrine (NAP) - PSUSA/00000629/201608

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Cetirizine is a second generation antihistamine and pseudoephedrine is a sympathomimetic substance of the phenethylamine and amphetamine classes. As a combination, cetirizine/pseudoephedrine is indicated in adults and children of 12 years of age and over for the treatment of symptoms associated with seasonal and perennial allergic rhinitis such as nasal congestion, sneezing, rhinorrhoea, nasal and ocular pruritus.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cetirizine/pseudoephedrine, 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 risk-benefit balance of cetirizine/pseudoephedrine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include acute generalised exanthematous pustulosis (AGEP), dyspnoea, eye disorders and erectile dysfunction as undesirable effects with an unknown frequency. In addition, anaphylactic shock should be added to the post marketing experience wording for immune systems disorders. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- In the next PSUR, the MAHs should closely monitor withdrawal syndromes and rebound effect. In addition, the MAH Johnson & Johnson should discuss the results of its PASS[30] on cardiovascular and neurological effects initiated in France in October 2013 as well as the signal of palpitations. The MAH UCB should discuss the ongoing signal of hepatitis.

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. Chlorquinaldol[31], promestriene (NAP) - PSUSA/00009272/201609

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

[29] 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
[30] PGRx-VASO: a post-marketing surveillance case crossover study on the impact of vasoconstrictors on the risk of myocardial infarction and stroke
[31] Vaginal tablet only

Chlorquinaldol is a halogenated hydroxyquinoline and promestriene, an oestradiol derivative. As a combination, chlorquinaldol/promestriene is indicated[32] for the treatment of atrophic vaginitis, leucorrhoea and oestrogen deficiency.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of chlorquinaldol/promestriene-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the occurrence of vaginal bleeding, to advise that the treatment with chlorquinaldol/promestriene vaginal tablets should be stopped and the aetiology of the bleeding investigated. In addition, vaginal bleeding should be added as an undesirable effect with an unknown frequency. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH(s) should provide any new data from all sources (spontaneous reports, reports from studies, published literature) in relation to systemic absorption of promestriene, as well as a review of all cases received that could be related to an increase in oestrogen level. In addition, the MAH(s) should discuss the importance of adequate tablet moistening in order to ensure a proper insertion of vaginal tablets and to determine whether the moisture degree plays a role in the risk of vaginal injury. Based on the findings, the MAH(s) should propose measures to reduce the risk of additional injuries as appropriate.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/LEG 071.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 071 [submission of a detailed review on vascular death, all-cause mortality, and main vascular events observed in RIDE (a phase III randomized study of ranibizumab injection in subjects with diabetic macular edema (DME)) and RISE (a phase III randomized study of ranibizumab injection in subjects with DME) as requested in the conclusions of PSUSA/00002609/201510 adopted by PRAC in April 2016] as per the request

[32] As vaginal tablets
[33] 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

for supplementary information (RSI) adopted in November 2016

Background

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). Lucentis (ranibizumab) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD), of visual impairment due to choroidal neovascularisation (CNV), of visual impairment due to diabetic macular oedema (DME) as well as for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), the PRAC requested the MAH to submit further data regarding cases of vascular death, all-cause mortality, and the main vascular events, observed in the RIDE[34] and RISE[35] studies. The responses were assessed by the Rapporteur for further PRAC advice. For background, see PRAC minutes April 2016 and PRAC minutes November 2016.

Summary of advice/conclusion(s)

- The PRAC did not consider that there was sufficient evidence to support an update of the product information regarding a possible increased risk for cardiovascular events associated with ranibizumab injections in the indication of visual impairment due to DME. While PRAC acknowledged that the data indicate small differences in the DME population with regard to the risk for arterial thromboembolic events, the Committee noted that there was no new emerging data prompting a change in the product information. The MAH should continue to monitor these issues as per routine pharmacovigilance.

7. Post-authorisation safety studies (PASS)

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

See Annex I 17.1.

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

See also Annex I 17.2.

7.2.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.2

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

[34] RIDE (CRFB002D4168g): Phase III randomized study of ranibizumab injection in subjects with clinically significant macular edema (ME) with centre involvement secondary to diabetes mellitus
[35] RISE (CRFB002D4170g): Phase III randomized study of ranibizumab injection in subjects with clinically significant ME with centre involvement secondary to diabetes mellitus
[36] In accordance with Article 107n of Directive 2001/83/EC
[37] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Scope: MAH's responses to MEA 003.1 [PASS protocol for study NB-451: a multinational, multicentre, prospective, non-interventional, PASS of prolonged-release naltrexone hydrochloride/bupropion hydrochloride for weight loss in the European Union (EU)] as per a request for supplementary information (RSI) adopted in October 2016

Background

Mysimba is a centrally authorised medicine containing naltrexone hydrochloride/bupropion hydrochloride (NB), a mu (μ)-opioid antagonist and a neuronal dopamine and norepinephrine reuptake inhibitor respectively, indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥ 30 kg/m2 (obese), or ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of one or more weight-related co-morbidities (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension).

As part of the RMP for Mysimba (naltrexone hydrochloride/bupropion hydrochloride), the MAH was required to conduct a category 3 PASS entitled 'a multinational, multicentre, prospective, non-interventional, PASS of prolonged-release naltrexone hydrochloride/bupropion hydrochloride (Mysimba) for weight loss in the European Union (EU)' in order to characterise the naltrexone hydrochloride/bupropion hydrochloride patient population and evaluate patterns of use, including potential off-label use. Further to the previous advice adopted at the October 2016 PRAC meeting, the MAH submitted an updated protocol (version 1.0) which was assessed by the Rapporteur. For further background, see PRAC minutes October 2016.

Summary of advice

- The PRAC, having considered the protocol version 1.0, with a chosen study design which follows a prospective single arm cohort design without comparator, objected to the draft protocol for the above listed medicinal product, as the Committee considered that the design of the study does not fulfil the study objectives that should mainly focus on aspects relating to compliance with the risk minimisation measures of Mysimba (naltrexone hydrochloride/bupropion hydrochloride).
- As an alternative, the PRAC recommended that the MAH for Mysimba conducts an observational retrospective database study based on secondary data analysis using existing databases (e.g. IMS) or other health claims databases (e.g. CPRD[38] for the UK). Therefore, the MAH should submit, within 90 days, a protocol synopsis for an observational retrospective database study based on secondary data analysis. This submission should be followed by 6-monthly updates of the corresponding feasibility assessments for the conduct of the study in European databases and the submission of the full study protocol once feasibility of the database study is established in the chosen EU databases based on feedback provided as per review of the feasibility assessments.

7.2.2. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a protocol for study C38072-AS-50027: a long-term non-interventional study comparing the risk of malignancy in severe asthma patients treated

[38] Clinical Practice Research Datalink

with reslizumab and patients not treated with reslizumab (RMP category 3)

Background

Cinqaero is a centrally authorised medicine containing reslizumab, a humanised monoclonal antibody (IgG4, κ), indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

As part of the RMP for Cinqaero (reslizumab), the MAH was required to conduct a category 3 PASS entitled 'a long-term non-interventional study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab (C38072-AS-50027)'. The study aims to compare the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using an existing healthcare database.

Summary of advice

- The study protocol version 1.0 for Cinqaero (reslizumab) could be acceptable provided that an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to EMA within 60 days.

7.3. Results of PASS imposed in the marketing authorisation(s)[39]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[40]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

None

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

[39] In accordance with Article 107p-q of Directive 2001/83/EC
[40] 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

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

None

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

8.1. Annual reassessments of the marketing authorisation

None

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also 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

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0007

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams; PRAC Co-rapporteur: Martin Huber

Scope: PRAC consultation on a type II variation consisting of an update of sections 4.3, 4.4 and 4.5 of the SmPC in order to add information on pharmacokinetic (PK) interactions with gemfibrozil and rifampicin in healthy subjects, based on the final clinical study report of the completed clinical pharmacology drug-drug interaction study AC-065-113. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update information on the hydrolysis of selexipag based on data from the previously submitted absolute bioavailability study AC-065-110 including minor amendments to sections 5.1 and 5.2 of the SmPC and to bring the product information (PI) in line with the latest QRD template (version 10)

Background

Selexipag is a selective IP[41] receptor agonist, distinct from prostacyclin and its analogues, indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO[42] functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.

A type II variation proposing to update the product information of Uptravi (selexipag) is under evaluation at the CHMP in order to reflect information on pharmacokinetic (PK) interactions with gemfibrozil and rifampicin in healthy subjects. The PRAC was requested to provide advice on this variation that includes a draft direct healthcare professional communication (DHPC).

Summary of advice

- Based on the review of the available information, the PRAC supported the distribution of a DHPC informing about the introduction of a new contraindication for the concomitant use of selexipag with strong inhibitors of CYP2C8[43]. The Committee reviewed and agreed the content of the DHPC as well as the communication plan.

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

None

10.3. Other requests

None

10.4. 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.

[41] Prostaglandin I2 receptor
[42] World Health Organization
[43] Cytochrome P4502C8

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Metformin (NAP)

Applicant: Merck (Glucophage, Stagid), various

PRAC Lead: Caroline Laborde

Scope: PRAC consultation on the assessment of the detailed review on the safety of metformin during pregnancy submitted to Member States following the request in the conclusion of PSUSA/00002001/201504 adopted by the PRAC in December 2015

Background

Metformin is a biguanide indicated for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy or in combination with other oral antidiabetic agents or with insulin.

In December 2015 as part of the recommendation of the PSUR single assessment (PSUSA) procedure for metformin (PSUSA/00002001/201504), the PRAC requested the MAH for the originator medicinal product containing metformin to submit to the EU NCAs within 180 days a comprehensive review on the safety of metformin during pregnancy. In the review, the MAH was requested to discuss any information regarding the metabolic control of pregnant diabetic women exposed to metformin and the potential impact on pregnancy outcome. A specific focus on off label use of metformin for the treatment of polycystic ovary syndrome was also requested in the context of pregnancy occurring while treated with metformin for this disease. For further background, see PRAC minutes December 2015.

In the context of the evaluation of the MAHs' submitted data, France 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 of France that the review does not show evidence of an increased risk of congenital abnormalities associated with metformin use during pregnancy.
- The PRAC advised that MAHs of metformin-containing products should be requested to continue routine pharmacovigilance activities and collect any adverse drug reactions (ADRs) reported in pregnant patients taking metformin and patients who become pregnant while taking metformin. In the next PSUR (DLP[44]: 01/04/2018), MAHs should provide a thorough review of all available data on pregnancy cases with metformin including data from epidemiological studies and literature. In addition, the MAHs should ensure that any reported pregnancy cases include information on the indications,

[44] Data lock point

glycaemic status of patients, exposure duration and the trimester of pregnancy. Moreover, the MAHs should include a discussion on off-label use of metformin in polycystic ovary syndrome (PCOS).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

12.2.1. EMA Scientific Co-ordination Board (SciCoBo) - update

PRAC lead: June Raine

Feedback from the last Scientific Co-ordination Board (SciCoBo) meeting held on 24 April 2017 was provided to PRAC. In addition, the EMA secretariat updated the PRAC on the recent information meeting with members of the EMA Management Board (MB) and Heads of NCAs (not represented at the MB) to address Brexit consequences. As an outcome of the discussion at PRAC, it was agreed to set up a PRAC ancillary working group focussing on Brexit preparedness, using expertise from the established 'GPAG', 'SMART' and 'PRAC working group on efficiency and effectiveness'. This working group will interact with the cross-Committee EMA working group on Committees' operational preparedness composed of EMA and Committees and NCAs representatives. Follow-up discussion is planned at PRAC in June 2017.

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

12.3.1. Healthcare Professionals' Working Party (HCPWP) – recommendation on additional risk minimisation measures (aRMMs)

PRAC lead: Almath Spooner, Sabine Straus

Following the joint Healthcare Professionals' Working Party (HCPWP) - Patients/Consumers Working Party (PCWP) workshop on risk minimisation measures (RMM) held in September 2015, a RMM 'topic group' was established within the HCPWP to reflect upon engagement with HCPs when designing RMMs. A set of high level recommendations was adopted by the HCPWP in March 2017. At the current meeting, the EMA/HCPWP secretariat presented to PRAC the HCPWP's proposal to embed into routine processes steps to support systematic consideration of early engagement of HCPs when discussing new additional RMMs and when reconsidering whether an additional RMM (aRMM) has become routine practice and the requirement can therefore be removed. PRAC agreed to set up a drafting group to determine criteria and consider potential operational issues for new marketing authorisation application (MAAs) processes and it suggested exploring further how to integrate HCPWP input in developing and implementing aRMMs. Special focus should be given to the

prevention of medication errors. Further discussion is provisionally planned in October 2017.

12.4. Cooperation within the EU regulatory network

12.4.1. PRAC strategic review and learning meeting, Estonia, 16-18 October 2017

PRAC lead: Maia Uusküla

The PRAC was presented with an outline of the preparation for the PRAC strategic review and learning meeting (SRLM) to be held on 16-18 October 2017 under the Estonian presidency of the Council of the EU.

12.5. Cooperation with International Regulators

None

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

12.6.1. EMA framework of collaboration with academia

The EMA Secretariat presented to PRAC the framework of collaboration between EMA and academia adopted by the EMA Management Board (MB) on 16 March 2017, together with an action plan. The framework describes objectives, scope and working methodology for the EMA collaboration with Academia (overall European structures and organisations), in line with the principles of transparency, independence and integrity, accountability, and broad representation. The PRAC emphasized the importance to ensure a good collaboration with EU NCAs in this initiative and ensure they are kept up-to-date. The PRAC expressed its support for the initiative and requested to be kept informed of further progress.

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

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

12.10.3. PSURs repository

None

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

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

Post-meeting note: following the PRAC meeting of May 2017, the updated EURD list was adopted by the CHMP and CMDh at their May 2017 meetings and published on the EMA website on 23/05/2017, see:

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

12.11. Signal management

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

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the May 2017 SMART Working Group (SMART WG) work stream WS1. As a follow-up to the April 2017 meeting, the WG WS1 discussed the handling of signals in the context of published (observational) studies and the need to exchange information within the network when the data do not fulfil the definition of a validated signal. The WS1 also discussed the updated proposal to circulate information on issues assessed by EU Member States that would not constitute a validated signal but could be of interest for the rest of the EU network. There was support for establishing clear criteria for the type of issues to be included in such communication in order to avoid confusion and achieve consistency. Moreover, the WG WS1 held a further discussion on the implementation of the requirement for MAHs to monitor EudraVigilance and to report validated signals after the go-live of EudraVigilance in November 2017 (see PRAC minutes April 2017 and under 12.11.2.).

12.11.2. Signal management – handling of MAHs' signals after the go-live of the new EudraVigilance system

PRAC lead: Sabine Straus

Following the April 2017 discussion, the PRAC further discussed the implementation of the requirement for MAHs to monitor EudraVigilance and to report validated signals after the go-live of EudraVigilance in November 2017 (see PRAC minutes April 2017), taking into account the feedback received from the European Commission (EC). The PRAC agreed that engagement with industry with respect to EudraVigilance monitoring tools should be taken forward to support smooth implementation. Further discussion will be scheduled at PRAC in due course.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring – experience analysis

Further to the implementation of the Pharmacovigilance legislation in 2012, additional monitoring has been introduced for medicines that are being monitored particularly closely by regulatory authorities and that have an inverted black triangle printed on the product information. In February 2017, the EMA Secretariat updated the PRAC on an ongoing project to analyse the experience with additional monitoring in preparation for an EC report mandated by the legislation. In April 2017, the PRAC reviewed the preliminary study outline. For further background, see PRAC minutes February 2017 and PRAC minutes April 2017. The aim of this study is to describe the experience with the use of the additional monitoring list since its creation in 2013 until December 2016, as well as to investigate whether the inclusion of a product on the additional monitoring list has an effect on reporting of ADRs. The collection of data and analysis will start in May 2017 for a report expected by end of 2017/beginning of 2018. The PRAC adopted the proposed study outline.

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

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

Post-meeting note: The updated additional monitoring list was published on 31/05/2017 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality- EudraVigilance auditable requirement project – recommendation on the independent final audit report

Taking into account the independent audit report, the PRAC considered that the EudraVigilance (EV) database meets the functional specifications drawn up pursuant to Article 24(2) first subparagraph of Regulation (EC) No 726/2004 and concluded that the EV database has achieved its full functionality for the purposes of Article 24(2) third subparagraph of Regulation (EC) No 726/2004. The PRAC adopted a recommendation to be forwarded to the EMA Management Board for further consideration.

The PRAC expressed the importance of testing the re-routing of reports to/from NCAs that should be available throughout the period until the new system becomes operative. As a next step and as requested by PRAC, the EMA Secretariat will prepare a EV technical support plan for NCAs in the EEA, which will include details of the re-routing testing with all NCAs, further technical instructions for the roll out of the new system as well as details on the launch of technical support webinars. The support plan for NCAs will be built in consultation with the Pharmacovigilance business team, EudraVigilance Expert Working Group (EV-EWG) members (NCA members) and IT Directors and will be subject to adoption by PRAC. The EV external compliance testing environment (XCOMP) will be launched to all stakeholders on 26 June 2017.

Furthermore, the EMA Secretariat confirmed the launch of the face-to-face training courses for experts from NCAs and for MAHs holders related to the new EV system functionalities and the use of the new ICH E2B(R3) ICSR format as of June 2017. The training calendar is published on the dedicated EMA EV webpage. Furthermore, for NCAs two EudraVigilance data analysis system (EVDAS) courses on a 'train the trainer' approach will be organised in October 2017. Communication planning at national level in support of the roll-out of the new system will be discussed at PRAC in July 2017. Finally, the EMA Secretariat will provide PRAC with a strategic development plan to cover 2018-2021 of operation of the new EV system.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

None

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[45]

14.1. 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[46].

14.1.1. Acetazolamide (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of acute generalized erythematous pustulosis (AGEP)

EPITT 18892 - New signal

Lead Member State(s): SE

14.1.2. Azithromycin (NAP), clarithromycin (NAP), erythromycin (NAP), roxithromycin (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18891 - New signal

Lead Member State(s): IE, IT, FI

14.1.3. Cladribine – LITAK (CAP); NAP

Applicant(s): Lipomed GmbH, various

PRAC Rapporteur: Patrick Batty

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 18875 – New signal

[45] 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

[46] 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

Lead Member State(s): UK

15. Annex I – Risk management plans

15.1. 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).

15.1.1. Efavirenz, emtricitabine, tenofovir disoproxil – EMEA/H/C/004240

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

15.1.2. Entecavir - EMEA/H/C/004377

Scope: Treatment of chronic hepatitis B virus (HBV) infection

15.1.3. Rituximab - EMEA/H/C/004723

Scope: Treatment of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)

15.1.4. Rituximab - EMEA/H/C/004724

Scope: Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA)

15.1.5. Rituximab - EMEA/H/C/004725

Scope: Treatment of non-Hodgkin's lymphoma (NHL), Granulomatosis with polyangiitis and microscopic polyangiitis

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

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

15.2.1. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0049

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 23) in order to amend the clinical study report (CSR) timelines, patient number and the primary and secondary endpoints listed in the EU RMP for study HGS1006-C1121/BEL114054: an ongoing phase 3, multicentre, multinational, randomized, double-blind, placebo-controlled 104-week treatment study to evaluate the efficacy and safety of intravenous (IV) belimumab 10 mg/kg plus standard of care (SOC) compared to placebo plus SOC in adult subjects with active lupus nephritis (LN)

15.2.2. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0095

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 28.0) in order to remove the post-authorisation measure (PAM) relating to the submission of an extension protocol to obtain additional long-term follow-up (LTFU) information from the paediatric population after patients complete a minimum of 5.5 year follow-up period as defined in the protocol of study BO20924 (BERNIE): an open-label, multicentre, randomized study of the safety and effect on event-free survival of bevacizumab in combination with standard chemotherapy in childhood and adolescent patients with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, as well as to amend the submission date of its final report (addendum clinical study report (CSR))

15.2.3. 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

15.2.4. Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/WS1160/0053; VOTUBIA (CAP) - EMEA/H/C/002311/WS1160/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II and the RMPs (version 13) to extend the due date for study CRAD001Y2201 (a phase 2 study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor positive (ER+) locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole) in the oncology setting

(Afinitor) from 3Q 2017 to Q1 2018 and for study CRAD001MIC03 (an international disease registry collecting data on manifestations, interventions, and outcomes in patients with tuberous sclerosis complex – TOSCA) in the tuberous sclerosis complex (TSC) setting (Votubia) from December 2017 to Q2 2018. Furthermore, the MAH took the opportunity to introduce some administrative changes to the RMP

15.2.5. 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

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

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

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

15.2.7. 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

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

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

15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0107

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information following the MAH's initiative to update its clinical trials safety database to include all currently completed clinical trials for both the intravenous (IV) and subcutaneous (SC) formulations. The adverse reactions' table in section 4.8 as well as the description of selected adverse reactions of special interest is amended. As a consequence, section 4.4 is brought in line with the amended section 4.8. The Package Leaflet and the RMP (version 22) are updated accordingly

15.3.2. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0043, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to add data from study C25007: a single-arm study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who are not suitable for stem cell transplantation or multi-agent chemotherapy. The submission of the clinical study report fulfils SOB 011 of the conditional marketing authorisation for Adcetris. The RMP (version 8.0) is updated accordingly

15.3.3. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0010

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the safety and efficacy findings of study A2303 (a phase III, multicentre, randomized, open label, study of oral *vs* standard chemotherapy in adult patients with anaplastic lymphoma kinase (ALK)-rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) who have been treated previously with chemotherapy (platinum doublet) and crizotinib) to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib. Annex II, the Package Leaflet, Labelling and the RMP (version 5) are updated accordingly

15.3.4. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0012

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include Zykadia as first-line treatment of adult patients

with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated to update the information based primarily on the supporting study CLDK378A2301 (ASCEND-4: a phase III multicentre, randomized study of oral ceritinib versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous NSCLC). The Package Leaflet and the RMP (version 6.0) are updated accordingly

15.3.5. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/WS1086/0034 Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/WS1086/0077

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final report for study GS-US-236-0140: a phase IV, randomized, open-label study evaluating the renal effect of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (DF) or other tenofovir DF-containing regimens (ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF or efavirenz/emtricitabine/tenofovir DF) compared to ritonavir-boosted atazanavir plus abacavir/lamivudine in antiretroviral treatment-naïve human immunodeficiency virus (HIV)-1 infected adults with an estimated glomerular filtration rate (eGFR)≥70 mL/min. The RMP (version 2.0) is updated accordingly

15.3.6. Daclizumab - ZINBRYTA (CAP) - EMEA/H/C/003862/II/0007

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add 'autoimmune haemolytic anaemia' with a frequency uncommon and to include a warning concerning symptoms of this adverse drug reaction. The Package Leaflet and the RMP (version 5.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial amendments throughout the Product Information

15.3.7. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0035

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to include 'liver function abnormalities' as an adverse event observed in the post-marketing setting and to clarify events not observed in placebo-controlled studies. The Package Leaflet and the RMP (version 8) are updated accordingly. The MAH has also taken the opportunity to make minor administrative changes in the Package Leaflet

15.3.8. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0036/G

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Grouped variation including: 1) submission of a clinical study report (CSR) for study 109HV321: a randomized, double-blind, phase 3b study to evaluate the safety and tolerability of BG00012 (dimethyl fumarate) when administered as 240 mg BID (twice daily) dose regimen with and without aspirin compared to placebo or following a slow titration (category 3); 2) submission of a CSR for study 109MS406 (ASSURE): a phase 4, randomized, double-blind study with a safety extension period to evaluate the effect of aspirin on flushing events in subjects with relapsing-remitting multiple sclerosis treated with Tecfidera (dimethyl fumarate) delayed-release capsules (category 4). The RMP (version 9.0) is updated accordingly

15.3.9. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0037

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of a clinical study report (CSR) for study 109MS307: an open-label study to assess the immune response to vaccination in Tecfidera-treated versus interferon-treated subjects with relapsing forms of multiple sclerosis (category 3). As a consequence, section 4.5 of the SmPC is updated. The Package Leaflet and the RMP (version 9.0) are updated accordingly

15.3.10. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/II/0079

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include the treatment of human immunodeficiency virus type 1 (HIV-1) infected adolescents, with nucleoside reverse transcriptase inhibitors (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years and weighing ≥ 35 kg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from study GS-US-236-0112 (a phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity through 48 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents). The Package Leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic amendments to the Product Information

15.3.11. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0135

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include pre-exposure prophylaxis of human immunodeficiency virus (HIV) infection in adolescents aged 12 to < 18 years at high risk. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects. The Package Leaflet and the RMP (version 15) are updated accordingly. In addition, the MAH took the opportunity to introduce minor linguistic

amendments to the Product Information

15.3.12. Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/II/0003/G

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations including: 1) introduction of a pre-filled cartridge as a new presentation for Rekovelle strength 12 µg/0.36mL; 2) addition of a new pack size for the strength 36 µg/1.08mL and addition of a new pack size for the strength 72 µg/2.16mL. As a consequence, sections 2, 4.2, 6.3, 6.5, 6.6 and 8 of the SmPC are updated. The Package Leaflet and the RMP (version 4.0) are updated accordingly

15.3.13. Icatibant - FIRAZYR (CAP) - EMEA/H/C/000899/II/0034/G, Orphan

Applicant: Shire Orphan Therapies GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variation including: 1) extension of indication to include adolescents and children over 2 years old for the use of Firazyr for symptomatic treatment of acute attacks of hereditary angioedema. As a consequence, section 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3; 2) update section 5.2 of the SmPC to reflect the effect of age (elderly), gender and race on pharmacokinetics of icatibant. The Package Leaflet and the RMP (version 6.0) are updated accordingly. All relevant pharmacokinetics studies have been previously assessed, as part of prior submissions

15.3.14. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0003, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include treatment of patients with Duchenne muscular dystrophy in whom respiratory function has started to decline and who are currently not taking concomitant glucocorticoids. The RMP (version 2.0) is updated accordingly

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

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Patrick Batty

Scope: Grouped variation including: 1) extension of indication of the approved chronic lymphocytic leukaemia (CLL) indication for Zydelig to include its use in combination with bendamustine and rituximab based on the results of the primary analysis of pivotal study GS-US-312-0115 (a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia). As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 2.2) are

updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet; 2) submission of the final clinical study report (CSR) for study 101-08 (a phase 2, single-arm study evaluated idelalisib monotherapy and in combination with rituximab in elderly subjects with previously untreated CLL or small lymphocytic lymphoma). Inclusion of this report provides additional safety data to support the evaluation of the use of idelalisib in patients with CLL and fulfilment of PAM008; 3) submission of the final clinical study report (CSR) for study GS-US-312-0123 (a phase 3 randomized study evaluated idelalisib in combination with bendamustine and rituximab in subjects with previously untreated CLL)

15.3.16. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC in order to update the information on use of Xultophy in patients with hepatic impairment based on clinical trial NN2211-1328 (a single-centre, open-label trial investigating the pharmacokinetics and the safety profile after a single dose of liraglutide in subjects with hepatic impairment and in subjects with normal hepatic function), the LEAD 1-6 meta-analysis as well as other liraglutide trials. In addition, 'fatigue' has been added to the tabulated list of adverse reactions in section 4.8 of the SmPC. The Package Leaflet and the RMP (version 6.0) are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.17. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/WS1158/0154/G; LIPROLOG (CAP) - EMEA/H/C/000393/WS1158/0117/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Grouped variation including: 1) addition of a pre-filled pen: Humalog and Liprolog 100 U/mL Junior KwikPen to administer insulin in half unit increments and containing insulin lispro 3mL cartridge already approved for use; 2) addition of a new pack size of 10 (2x5) pre-filled pens (multipack) for Humalog and Liprolog 100 U/mL Junior KwikPen, including insulin lispro 3mL cartridge already approved for use.; 3) update of sections 4.2 and 4.4 of the SmPC of the already authorised 100 U/mL Humalog and Liprolog presentations to include the paediatric population. The Package Leaflet and the RMP (version 8.0) are updated accordingly

15.3.18. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0042

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the final results of study CA184-169: a randomized double-blind phase III study of ipilimumab administered at 3 mg/kg versus at 10 mg/kg in subjects previously treated or untreated with unresectable or metastatic melanoma, in order to fulfil ANX 014.1. The MAH also provided with this

variation application efficacy and safety data from study CA184-169 in two subgroups: female ≥ 50 years of age and with brain metastases in order to fulfil MEA 015.1. Annex II.D 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, to include some editorial changes and correct some typos throughout the product information, and to bring the product information in line with the latest QRD template (version 10)

15.3.19. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0002, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC to reflect the final overall survival analysis of C16010 China continuation study, a phase 3 study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide in patients with relapsed and/or refractory multiple myeloma, in order to fulfil specific obligation (SOB) 002. Annex II.E and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to make a small correction in sections 4.7 and 9 of the SmPC and to the German translations

15.3.20. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0065/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Qun-Ying Yue

Scope: Grouped variations including an extension of indication to include monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in children from 4 to less than 16 years old with epilepsy. For the treatment initiation pack, it is proposed to extend only the adjunctive treatment to adolescents weighting more than 50 kg (not suitable for monotherapy and children and adolescents weighting less than 50 kg). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 12) are updated accordingly. In addition, the MAH took the opportunity to bring Annex III-A in line with the latest QRD template (version 10) and to introduce combined SmPC for film coated tablets. Furthermore, sections 6.3 and 6.5 of the SmPC for the syrup presentation only are updated due to the extension of shelf life of the finished product after first opening from 4 weeks to 6 months and addition of a 10 mL dosing syringe for syrup, as an additional dosing device to use in the paediatric population

15.3.21. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/II/0161/G

Applicant: AbbVie Ltd.

PRAC Rapporteur: Caroline Laborde

Scope: Grouped variation including: 1) extension of indication to include children aged 14 days and older in the treatment of human immunodeficiency virus (HIV)-1. As a consequence, sections 4.1, 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC are updated. The studies provided in support of the paediatric indication are part of the agreed PIP decision P/0144/2012. In addition, the MAH further updated section 4.4 to add information regarding

the use of Kaletra oral solution with feeding tubes. The Package Leaflet, Labelling and RMP (version 8) are updated accordingly; 2) addition of a new pack size of 120 mL in (2 x 60mL bottles) for Kaletra 80mg/mL and 20 mg/mL oral solution (EU/1/01/172/003); 3) addition of a new 2 mL oral dose syringe for the 120 mL presentation

15.3.22. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/II/0017

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to reflect the long-term safety and efficacy data from study VX12 809 105: a phase 3, rollover study to evaluate the safety and efficacy of long term treatment with lumacaftor/ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the F508del cystic fibrosis transmembrane conductance regulator (CFTR) mutation (MEA 001). The RMP (version 2.7) is updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.23. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0032

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to add administration guidance and update the safety information based on final results from imposed PAES CA209067: an interventional, randomized, double-blind study in subjects treated with nivolumab monotherapy, ipilimumab monotherapy and nivolumab combined with ipilimumab. Annex II, the Package Leaflet and the RMP (version 5.8) are updated accordingly. This submission fulfils ANX 016. In addition, the MAH took the opportunity to introduce minor editorial and formatting revisions in the Product Information

15.3.24. Obinutuzumab - GAZYVARO (CAP) - EMEA/H/C/002799/II/0016, Orphan

Applicant: Roche Registration Limited

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include an indication in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response for the treatment of patients with previously untreated advanced follicular lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (version 3.0) are updated accordingly. In addition, the due date for provision of the final clinical study report for study BO21223/GALLIUM, a multicentre, phase 3, open-label, randomized study in previously untreated patients with advanced indolent non-Hodgkin's lymphoma evaluating the benefit of obinutuzumab plus chemotherapy compared to rituximab plus chemotherapy followed by obinutuzumab or rituximab maintenance therapy in responders, listed in the RMP as a category 3 is updated. Furthermore, the Product Information is brought in line with the missing information of QRD template (version 9.1). The MAH took the opportunity to introduce some clarification/editorial changes to the SmPC for accuracy and clarity

15.3.25. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0023/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation including: 1) extension of indication to add the treatment of urothelial carcinoma in patients previously treated with chemotherapy based on the results from study KEYNOTE-045, a phase 3, randomized, active-controlled, multi-site, open-label trial evaluating pembrolizumab administered at 200 mg Q3W versus investigators' choice of paclitaxel, docetaxel, or vinflunine in patients previously treated with chemotherapy; 2) extension of indication to add the treatment of urothelial carcinoma in patients ineligible for cisplatin (not previously treated) based on the results from study KEYNOTE-52, a phase 2, single-arm, multisite, open-label trial of pembrolizumab at 200 mg Q3W in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Furthermore, the MAH is proposing a change to section 4.3 of the SmPC to add that only patients with severe hypersensitivity should be excluded from therapy, and a change to section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions. The Package Leaflet and the RMP (version 7.0) are updated accordingly

15.3.26. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/X/0059

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new strength of 600mg film-coated tablets. The RMP (version 11.0) is updated accordingly

15.3.27. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/II/0020

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with one systemic 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 RMP (version 5.0) are updated accordingly. Furthermore, the Product Information is brought in line with the latest QRD template (version 10.0)

15.3.28. Rituximab - TRUXIMA (CAP) - EMEA/H/C/004112/II/0002/G

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) change in pack size of the finished product: change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal product, including biological/immunological medicinal products. The RMP (version 6) is updated accordingly. The RMP (version 6) is also updated to harmonise

the safety concerns sections with the latest RMP for the reference product

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

Applicant: Bayer Pharma 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 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

15.3.30. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/WS0965/0035; Sevelamer - SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS0965/0007

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension of indication to include the control of hyperphosphataemia in paediatric patients (>6 years of age and a body surface area (BSA) of >0.75 m^2) with chronic kidney disease. As a consequence, section 4.2 of the SmPC is updated to detail the posology in the paediatric patients. The Package Leaflet and the RMP (version 8.0) are updated accordingly

15.3.31. 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

15.3.32. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/II/0036

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add the treatment of chronic hepatitis C in adolescents aged 12 to <18 years. 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 information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet and the RMP (version 5.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Product Information is brought in line with the latest QRD template (version 10)

15.3.33. 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[47]

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

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

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

16.1. PSUR procedures including centrally authorised products only

16.1.1. Alipogene tiparvovec - GLYBERA (CAP) - PSUSA/00010056/201610

Applicant: uniQure biopharma B.V., ATMP[48]

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[47] World Health Organization
[48] Advanced Therapy Medicinal Product

16.1.2. Aliskiren - RASILEZ (CAP); aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - PSUSA/00000089/201609

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.3. Bazedoxifene - CONBRIZA (CAP) - PSUSA/00000302/201610

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.4. Buprenorphine, naloxone - SUBOXONE (CAP) - PSUSA/00002113/201609

Applicant: Indivior UK Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.5. Choriogonadotropin alpha - OVITRELLE (CAP) - PSUSA/00000736/201609

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Defibrotide - DEFITELIO (CAP) - PSUSA/00010086/201610

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.7. Delamanid - DELTYBA (CAP) - PSUSA/00010213/201610

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.8. Eculizumab - SOLIRIS (CAP) - PSUSA/00001198/201610

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.9. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/201610 (with RMP)

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.10. Granisetron[49] - SANCUSO (CAP) - PSUSA/00010101/201610

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.11. Idarucizumab - PRAXBIND (CAP) - PSUSA/00010435/201610

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.12. Insulin aspart - NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/00001749/201609

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.13. Insulin degludec - TRESIBA (CAP); insulin degludec, insulin aspart - RYZODEG (CAP) - PSUSA/00010036/201609

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.14. Insulin glargine - ABASAGLAR (CAP); LANTUS (CAP); TOUJEO (CAP) - PSUSA/00001751/201610

Applicant: Eli Lilly Regional Operations GmbH (Abasaglar), Sanofi-aventis Deutschland GmbH (Lantus, Toujeo)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

[49] Transdermal patch only

16.1.15. Macitentan - OPSUMIT (CAP) - PSUSA/00010115/201610

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.16. Meningococcal group A, C, W135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/201610

Applicant: Pfizer Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.17. Micafungin - MYCAMINE (CAP) - PSUSA/00002051/201610

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.18. Miglustat - ZAVESCA (CAP) - PSUSA/00002062/201610

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.19. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/201610

Applicant: Helsinn Birex Pharmaceuticals Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.20. Ocriplasmin - JETREA (CAP) - PSUSA/00010122/201610

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.21. Ofatumumab - ARZERRA (CAP) - PSUSA/00002202/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.22. Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) – FOCLIVIA (CAP); prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - PSUSA/00010008/201610

Applicant: Seqirus S.r.l

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.23. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/201609

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.24. Para-aminosalicyic acid[50] - GRANUPAS (CAP) - PSUSA/00010171/201610

Applicant: Lucane Pharma

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.25. Pasireotide - SIGNIFOR (CAP) - PSUSA/00009253/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.26. Pazopanib - VOTRIENT (CAP) - PSUSA/00002321/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.27. Pitolisant - WAKIX (CAP) - PSUSA/00010490/201609

Applicant: BIOPROJET PHARMA

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.28. Posaconazole - NOXAFIL (CAP) - PSUSA/00002480/201610

Applicant: Merck Sharp & Dohme Limited

[50] Centrally authorised product

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.29. Prucalopride - RESOLOR (CAP) - PSUSA/00002568/201610

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Ramucirumab - CYRAMZA (CAP) - PSUSA/00010323/201610

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.31. Ranibizumab - LUCENTIS (CAP) - PSUSA/00002609/201610

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Siltuximab - SYLVANT (CAP) - PSUSA/00010254/201610

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.33. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/201610

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.34. Tocilizumab - ROACTEMRA (CAP) - PSUSA/00002980/201610

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201610

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.36. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/201609

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Brinzolamide - AZOPT (CAP); NAP - PSUSA/00000432/201608

Applicants: Alcon Laboratories (UK) Ltd (Azopt), various

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Biperiden (NAP) - PSUSA/00000415/201608

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Drospirenone, ethinylestradiol (NAP) - PSUSA/00010217/201609

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.3. Esketamine (NAP) - PSUSA/00001266/201608

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.3.4. Estradiol[51] (NAP) - PSUSA/00010440/201608

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. Germanium (^{68}Ge) chloride, gallium (^{68}Ga) chloride (NAP) - PSUSA/00010364/201609

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.6. Ketoprofen[52] (NAP) - PSUSA/00009205/201609

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.7. Latanoprost[53] (NAP) - PSUSA/00001834/201610

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.8. Oxcarbazepine (NAP) - PSUSA/00002235/201608

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.9. Penciclovir (NAP) - PSUSA/00002333/201608

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

[51] Except cream, balm, emulsion for application in female genital area
[52] Topical use only
[53] Paediatric indications only

16.3.10. Pilocarpine[54] (NAP) - PSUSA/00002410/201608

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Tolterodine (NAP) - PSUSA/00002993/201609

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.12. Tuberculin purified protein derivative (NAP) - PSUSA/00003063/201609

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/LEG 029.1

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 029 [submission of a safety assessment of all haemorrhagic events for cinacalcet events in all controlled clinical studies with cinacalcet, irrespective of indication as requested in the conclusions of EMEA/H/C/PSUSA/00000756/201602 adopted by the PRAC on 29 September 2016] as per the request for supplementary information (RSI) adopted in January 2017

16.4.2. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/LEG 030

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a detailed review of drug-related hepatic disorders as requested in the conclusions of EMEA/H/C/PSUSA/00000756/201602 adopted by the PRAC on 29 September 2016

[54] Ophthalmic formulation only

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

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

17.1. Protocols of PASS imposed in the marketing authorisation(s)[55]

17.1.1. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/PSA/S/0009.1

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Submission of a revised PASS protocol following substantial amendments for study MA25101: an observational cohort study of the safety of brentuximab vedotin in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) as per the request for supplementary information (RSI) adopted in December 2016

17.1.2. Hydroxyethyl starch (NAP) - EMEA/H/N/PSA/S/0011.1

Applicant: B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of a revised PASS protocol for a retrospective drug utilisation study (DUS) (ENCEPP/SDDP/12540) to investigate the routine use of hydroxyethyl starch (HES)-containing infusion solutions of B.Braun in hospitals settings as per the request for supplementary information (RSI) adopted in January 2017

17.1.3. Teicoplanin (NAP) - EMEA/H/N/PSA/S/0013.1

Applicant: Sanofi-aventis (Targocid)

PRAC Rapporteur: Valerie Strassmann

Scope: Revised protocol following substantial amendments for a PASS study: a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data as per the request for supplementary information (RSI) adopted in February 2017

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[56]

17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.2

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of a revised PASS protocol for study OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (RMS) as per the request for supplementary information (RSI) adopted in December 2016

17.2.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 008 [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in December 2016

17.2.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 007 [assessment of a retrospective, observational cohort study protocol, using four administrative claims databases, to assess the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus (T2DM) treated with canagliflozin-containing medicines or other antihyperglycemic agents], as per request for supplementary information (RSI) adopted in December 2016

17.2.4. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 001.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA-001 [submission of an updated protocol for PASS L01XC24: a survey measuring the effectiveness of the educational materials regarding the minimisation of risk of interference for blood typing with daratumumab] as per request for supplementary information (RSI) adopted in December 2016

[56] 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

17.2.5. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045 [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency virus (HIV)-1 uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber, as a result of variation II/0126 finalised at CHMP/PRAC in July 2016 to extend the indication to PrEP] as per request for supplementary information (RSI) adopted in January 2017

17.2.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study MK-8259-050: an observational PASS of golimumab in treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR) as requested in the conclusions of variation procedure II/63

17.2.7. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 047.3

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to MEA 047.2: MAH's responses to MEA 047.2 [PASS protocol and statistical analysis plan for study HUBIN-C-06380: a prospective cohort study organised as exposure registry] as per request for supplementary information (RSI) adopted in June 2016

17.2.8. Lipegfilgrastim - LONQUEX (CAP) - EMEA/H/C/002556/MEA 004.2

Applicant: Sicor Biotech UAB

PRAC Rapporteur: Patrick Batty

Scope: Updated PASS protocol for study XM22-ONC-50002: a multi-country, multicentre, retrospective observational study to describe the pattern of lipegfilgrastim use, and specifically to quantify the extent of lipegfilgrastim off-label use in routine clinical practice in several countries of the EU to reflect a revised list of countries

17.2.9. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004.2

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 004.1 [revised PASS protocol for study NB-452: a survey to evaluate the effectiveness of the physician prescribing checklist (PPC) among physicians in the EU] as per request for supplementary information (RSI) adopted in September 2016

17.2.10. Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/MEA 001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Submission of a protocol for study I5B-MC-B001: an observational PASS to evaluate the safety and effectiveness of olaratumab in combination with doxorubicin in patients with advanced soft tissue sarcoma (STS) including rare subtypes (as requested in the conclusions of the initial MAA)

17.2.11. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 003.1

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003 [PASS protocol for study AC-065A403 to evaluate risk minimisation measures for mEDication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in Clinical prAcTicE (EDUCATE)], as per request for supplementary information (RSI) adopted in December 2016

17.2.12. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 025.1

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 025 [PASS protocol: to evaluate the effectiveness of risk minimisation measures: a survey among healthcare professionals and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa in six European countries], as per request for supplementary information (RSI) adopted in December 2016

17.2.13. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002

Applicant: AbbVie Ltd.

PRAC Rapporteur: Patrick Batty

Scope: Submission of a protocol for a prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients

17.3. Results of PASS imposed in the marketing authorisation(s)[57]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[58]

17.4.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0108/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations including 1) submission of the final clinical study report from epidemiological IM101045A study: safety of non-biologic disease-modifying antirheumatic drugs (DMARDs) and biologic treatment for rheumatoid arthritis (RMP category 3 study); 2) submission of the final clinical study report from epidemiological IM101045B study: safety and outcomes in patients treated with abatacept and other anti-rheumatic therapies (RMP category 3 study). IM101045A and IM101045B are both observational studies, sharing overlapping safety objectives (assessment of the risk of infections, infusion-related reactions, autoimmune disorders, injection reactions and combination use). The RMP (version 22) is updated accordingly

17.4.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0159

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) for study P06-134: a long-term non-interventional registry to assess safety and effectiveness of Humira in subjects with moderately to severely active Crohn's disease in fulfilment of MEA 056.9

17.4.3. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0162

Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final national report for the biologics registry: Anti-Rheumatic Treatment in Sweden (ARTIS) after ending AbbVie's support by end 2015 in fulfilment of MEA 066.5

17.4.4. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/II/0100

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final report for study 1160.144 evaluating the potential off-label

[57] In accordance with Article 107p-q of Directive 2001/83/EC
[58] 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

use of dabigatran etexilate in Europe: a drug utilisation study (DUS) in Cegedim France, Denmark, and UK in Clinical Practice Research Datalink (CPRD)

17.4.5. Human rotavirus, live attenuated - ROTARIX (CAP) - EMEA/H/C/000639/II/0094

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for EPI-ROTA-007 VS US DB: a phase 4, open, observational study of the safety of Rotarix, administered to a birth cohort in US States health insurance plans. The RMP (version 17) is updated in order to amend information in relation to EPI-ROTA-007 VS US DB study, EPI-ROTA-052 BOD EU SUPP (an observational community-based strain surveillance study) as agreed in the conclusions of variation II/86. In addition, the MAH took this opportunity to further update the RMP with the new due date for submission of the final study report for ROTA-085 PMS (a special drug use investigation for Rotarix (investigation of incidence of intussusception after vaccination for rotavirus gastroenteritis) conducted with the objective to determine the incidence of intussusception after vaccination with Rotarix in Japan)

17.4.6. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0064

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final study report for study MI-MA194: a post-marketing observational evaluation of the safety of Fluenz in children and adolescents with high-risk conditions

17.4.7. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0092

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final report from a systematic review and individual patient data meta-analysis of peginterferon alfa-2a (PEG-IFN) studies to identify optimal stopping rules in order to provide the final outcome related to the assessment of a response guided therapy (RGT) for Pegasys in hepatitis B virus (HBV)-infected patients

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

Applicant: Eisai Ltd

PRAC Rapporteur: Claire Ferard

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

17.4.9. Saxagliptin - ONGLYZA (CAP) - EMEA/H/C/001039/WS0960/0040/G saxagliptin, metformin hydrochloride - KOMBOGLYZE (CAP) - EMEA/H/C/002059/WS0960/0033/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Group of variations consisting of final epidemiological study results for studies D1680R00011 (a cohort study comparing risk of major cardiovascular (CV) events between patients with type 2 diabetes mellitus (T2DM) who are new initiators of saxagliptin and those who are new initiators of oral antidiabetic drug (OAD) treatments in classes other than DPP-4 inhibitors), D1680R00012 (a cohort study comparing risk of hospitalization with acute liver failure between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00013 (a cohort study comparing risk of hospitalization with infections between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments), D1680R00014 (a cohort study comparing risk of hospitalization for severe hypersensitivity (including severe cutaneous reactions) between patients with T2DM exposed to saxagliptin and those exposed to other OAD treatments) and D1680R00015 (a cohort study comparing risk of hospitalization for acute kidney injury between patients with T2DM initiating saxagliptin and those initiating other OAD treatments), and consequent update of the RMP. As a consequence, the RMP (version 11) is updated accordingly. In addition, routine changes are made in parts III (pharmacovigilance plan, overview of planned pharmacovigilance actions) and IV. A safety review based on the literature is also included to investigate acute kidney injury associated with saxagliptin, saxagliptin and metformin at requested by PRAC

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[59]

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.3

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Second annual progress report for PASS OBS13434: a prospective, multicentre, observational, PASS to evaluate the long term safety profile of alemtuzumab treatment in patients with relapsing forms of multiple sclerosis (MS) with the aim to better characterize the long-term safety profile of alemtuzumab in relapsing MS patients and to determine the incidence of adverse events of special interest (AESIs)

17.5.2. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.9

Applicant: Pfizer Limited

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

PRAC Rapporteur: Martin Huber

Scope: Fourth annual interim report for the period October 2015 to October 2016 of EU PASS B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe

17.5.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.17

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual interim report for study BEL115467/HGS1006-C1113: a randomized, double-blind placebo-controlled large safety study evaluating the incidence of all-cause mortality and adverse events of special interest (including serious infections, malignancies, serious infusion and hypersensitivity reactions and serious psychiatric events) in patients with systemic lupus erythematosus

17.5.4. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 006

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB 102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology observational study assessing the risk of severe complications of urinary tract infections (UTI) between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.5. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 007

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure/kidney injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 008

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure/acute liver injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.7. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB 102-118ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology observational study assessing the risk of cancer between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.8. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 001.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB 102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology observational study assessing the risk of severe complications of urinary tract infections (UTI) between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.9. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 002.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure/kidney injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.10. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 003.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure/acute liver injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.11. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.5

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: First interim report for study MB 102-118ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology observational study assessing the risk of cancer between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.12. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB 102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology observational study assessing the risk of severe complications of urinary tract infections (UTI) between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.13. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 006

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure/kidney injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.14. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 007

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure/acute liver injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.15. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 008

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB 102-118ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology observational study assessing the risk of cancer between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.16. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 008

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB 102-103 ST/D1690R00008 - (EUPAS12113): a pharmacoepidemiology observational study assessing the risk of severe complications of urinary tract infections (UTI) between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.17. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 009

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB102-110 ST/D1690R00004 - (EUPAS11684): a pharmacoepidemiology observational study assessing the risk of acute renal failure/kidney injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.18. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 010

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB102-104 ST/D1690R00005 - (EUPAS12110): a pharmacoepidemiology observational study assessing the risk of acute hepatic failure/acute liver injury between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.19. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 011

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: First interim report for study MB 102-118ST/D1690R00007 - (EUPAS12116): a pharmacoepidemiology observational study assessing the risk of cancer between patients with type 2 diabetes mellitus (T2DM) exposed to dapagliflozin and those exposed to other antidiabetic treatments

17.5.20. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/MEA 001.1

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Second interim annual report for EuroSIDA PASS study 201177: a prospective observational cohort study in patients receiving dolutegravir (category 3) to investigate the risk of hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

17.5.21. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/MEA 007.1

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Second interim report for EuroSIDA PASS study 201177DTG: a prospective observational cohort study to monitor the occurrence of hypersensitivity reaction and hepatotoxicity in patients receiving dolutegravir (category 3) to investigate the risk of

hypersensitivity reactions (HSR), hepatotoxicity and serious rash (division of acquired immune deficiency syndrome (DAIDS) grading scale category 3 or 4)

17.5.22. Insulin human - INSUMAN (CAP) - EMEA/H/C/000201/MEA 041

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: First annual interim study report of the Insuman implantable registry HUBIN-C-06380: a European observational cohort of patients with type 1 diabetes treated via intraperitoneal route with Insuman implantable 400 IU/mL in Medtronic MiniMed implantable pump

17.5.23. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.2

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: First biennial interim results for study TED-R-13-002: an international Short bowel syndrome registry: a prospective, long-term observational cohort study of patients with short bowel syndrome

17.5.24. Turoctocog alfa - NOVOEIGHT (CAP) - EMEA/H/C/002719/MEA 004.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 004.1 [Submission of an interim report for the post-authorisation safety study NN7008-3553, a multicentre non-interventional study of safety and efficacy of turoctocog alfa (recombinant factor VIII (rFVIII)) during long-term treatment of severe and moderately severe haemophilia A (FVIII ≤2%)] as per request for supplementary information (RSI) adopted in January 2017

17.5.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.12

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Annual report for PSOLAR (PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry program designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics

17.6. 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.

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

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

18.1. Annual reassessments of the marketing authorisation

None

18.2. Conditional renewals of the marketing authorisation

18.2.1. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - EMEA/H/C/002801/R/0003 (without RMP)

Applicant: MolMed SpA, ATMP[60]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/R/0033 (with RMP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Claire Ferard

Scope: 5-year renewal of the marketing authorisation

18.3.2. Copper (^{64}Cu) chloride - CUPRYMINA (CAP) - EMEA/H/C/002136/R/0014 (with RMP)

Applicant: Sparkle S.r.l.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

[60] Advanced therapy medicinal product

18.3.3. Glycopyrronium bromide - SEEBRI BREEZHALER (CAP) - EMEA/H/C/002430/R/0020 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.4. Glycopyrronium bromide- TOVANOR BREEZHALER (CAP) - EMEA/H/C/002690/R/0022 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.5. Glycopyrronium bromide - ENUREV BREEZHALER (CAP) - EMEA/H/C/002691/R/0020 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.6. 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

18.3.7. Ingenol mebutate - PICATO (CAP) - EMEA/H/C/002275/R/0023 (with RMP)

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.8. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/R/0032 (without RMP)

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: 5-year renewal of the marketing authorisation

18.3.9. Memantine hydrochloride - MEMANTINE MERZ (CAP) - EMEA/H/C/002711/R/0012 (without RMP)

Applicant: Merz Pharmaceuticals GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.10. 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

18.3.11. Temsirolimus - TORISEL (CAP) - EMEA/H/C/000799/R/0065 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 2-5 May 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Yuliyan Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	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
Claire Ferard	Member	France	No interests declared	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
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
John Joseph Borg	Alternate	Malta	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
Helga Haugom Olsen	Member	Norway	No interests declared	Full involvement
Kristin Thorseng	Alternate	Norway	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kvande			declared	
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sanches de Castro Lopes Silva	Alternate	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
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
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'	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		Representative	applicable to this meeting	
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Cécile Lescrainier	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Christelle Bizimungu	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Predrag Tadinac	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Marina Lesičar	Expert - via telephone*	Croatia	No interests declared	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No participation in discussion, final deliberations and voting on:	4.2.1 Insulin-containing products; 5.3.17. Insulin degludec, liraglutide - XULTOPHY (CAP); 5.3.22. Liraglutide - VICTOZA (CAP); 6.1.17. Insulin aspart - NOVOMIX (CAP); NOVORAPID (CAP); 6.1.18. Insulin degludec, liraglutide - XULTOPHY (CAP); 6.1.19. Insulin degludec - TRESIBA (CAP); insulin degludec, insulin aspart - RYZODEG (CAP); 7.5.24. Turoctocog alfa - NOVOEIGHT (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jukka Sallinen	Expert - in person*	Finland	No restrictions applicable to this meeting	Full involvement
Mehdi Benkebil	Expert - via telephone*	France	No interests declared	Full involvement
Celine Druet	Expert - via telephone*	France	No interests declared	Full involvement
Nathalie Dumarcet	Expert - via telephone*	France	No interests declared	Full involvement
Muriel Echemann	Expert - via telephone*	France	No interests declared	Full involvement
Marie Gadeyne	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
David Benee Olsen	Expert - in person*	Norway	No restrictions applicable to this meeting	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Monika Trojan	Expert - via telephone*	Poland	No interests declared	Full involvement
Peter Koreň	Expert - in person*	Slovakia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Carin Bergquist	Expert - in person*	Sweden	No interests declared	Full involvement
Åsa Kjellström	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Charlotte Söderberg Nyhem	Expert - in person*	Sweden	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Phil Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Valerie Joynson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Sarah Mee	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	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: www.ema.europa.eu/