5 May 2017
EMA/PRAC/271304/2017
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 3-6 April 2017

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 3-6 April 2017 meeting by welcoming all participants.

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

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

1.2. Agenda of the meeting on 3-6 April 2017

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

1.3. Minutes of the previous meeting on 6-9 March 2017

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

Post-meeting note: the PRAC minutes of the meeting held on 6-9 March 2017 were published on the EMA website on 5 May 2017 (EMA/PRAC/287540/2017).

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

None

3.3. Procedures for finalisation

None

3.4. Article 5(3) of Regulation (EC) No 726/2004: PRAC advice on CHMP request

See 10.3.1. Other safety issues for discussion requested by the CHMP or the EMA - Others

3.5. Others

3.5.1. 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: Mallinckrodt Deutschland GmbH (Optimark); various

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

Scope: Request for re-examination of the review of the benefit-risk balance 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 marketing authorisation holders concerned by this referral procedure requested a re-examination. 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 and PRAC minutes March 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[1], expected to conclude in July 2017.

Discussion

The PRAC noted the notification letters from some of the MAHs concerned by this referral procedure to request a re-examination of the recommendation adopted by the PRAC in March 2017.

The PRAC appointed Ulla Wändel Liminga as Rapporteur and Valerie Strassmann as Co-Rapporteur for the re-examination procedure.

Summary of recommendation(s)/conclusions

The Committee agreed on a preliminary timetable for the re-examination procedure expected to conclude in July 2017. The timetable will be finalised further to the receipt of the MAHs' grounds for re-examination of the PRAC recommendation.

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/SDA/010

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Signal of acute kidney injury

EPITT 18778 – Follow up to December 2016

[1] Under Article 32 of Directive 2001/83/EC

[2] 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

Background

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

Discussion

Having considered the evidence from case reports in EudraVigilance as well as the cumulative review of information from all completed and ongoing clinical trials and post-marketing cases regarding the worsening of renal function and cases of (acute) renal failure, after the initiation of albiglutide, and the review of the available literature exploring potential mechanisms provided by the MAH, the PRAC agreed that the MAH of Eperzan (albiglutide) should submit a variation to amend the product information to include a warning on the risk of dehydration, sometimes leading to renal impairment and acute renal failure.

Summary of recommendation(s)

- The MAH for Eperzan (albiglutide) should submit to EMA, within 60 days, a variation for amending the product information[3].

For the full PRAC recommendation, see EMA/PRAC/221998/2017 published on 21/04/2017 on the EMA website.

4.3.2. Docetaxel – TAXOTERE (CAP), DOCETAXEL ACCORD (CAP), TAXESPIRA (CAP)

Applicant(s): Aventis Pharma S.A. (Taxotere), Accord Healthcare Ltd (Docetaxel Accord), Hospira UK Limited (Taxespira), various

PRAC Rapporteur: Claire Ferard

Scope: Signal of unexpected seriousness of reported adverse drug reactions (ADRs) with docetaxel in particular neutropenic enterocolitis and suspicion of an increase in ADR reporting rate in France with docetaxel-containing products

EPITT 12059 – Follow up to March 2017

Background

The PRAC discussed the EMA detailed analysis of the data from EudraVigilance on adverse reactions related to neutropenia and related disorders associated with docetaxel from January 2003 onwards alongside the analysis performed by the French regional centre of pharmacovigilance of Toulouse on the signal of unexpected seriousness of reported adverse drug reactions with docetaxel in particular neutropenic enterocolitis and suspicion of an increase in ADR reporting rate in France with docetaxel-containing products. For background information, see PRAC minutes March 2017.

Discussion

Having considered the available evidence namely, the extended analysis performed in EudraVigilance and the analysis of the French data, the PRAC agreed that this signal should be further explored and the updated report of the French data should be brought back to the Committee in June 2017.

[3] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

Summary of recommendation(s)

- The signal of unexpected seriousness of reported ADRs with docetaxel in particular neutropenic enterocolitis and suspicion of an increase in ADRs reporting rate in France with docetaxel-containing products will be further explored at the June 2017 PRAC meeting with the updated report of the French regional pharmacovigilance centre of Toulouse.

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

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of hyponatremia

EPITT 18631 – Related to March 2016

Background

Previously a non-urgent information (NUI) request was circulated by Denmark to learn from the experiences and best practices within the different EU Member States for raising awareness among healthcare professionals regarding the risk of hyponatremia associated with use of physiologically intravenous (IV) fluids, and strategies to minimise the risk. Along with a cumulative review of the literature and a search and analysis of data retrieved from EudraVigilance, the signal of hyponatremia with intravenous fluids containing electrolytes and/or carbohydrates was further discussed by the PRAC at Denmark's request. For background information, see PRAC minutes March 2016.

Discussion

Having considered the evidence from EudraVigilance as well as from the literature, the PRAC agreed that this issue merited further investigation. To have a full overview of the available evidence as well as for completeness, the Committee considered that a further analysis of data available in EudraVigilance should be performed. The analysis would encompass hyponatremia-related terms and would look into the overall reporting rates for involved products as well as disproportionality of reporting, different age groups including children and several other variables (e.g. co-medication).

The PRAC appointed Doris Stenver as Rapporteur for the signal.

Summary of recommendation(s)

- The signal of hyponatremia will be further explored at the June 2017 PRAC meeting with the analysis of data available in EudraVigilance, along with a proposed wording to be included in the product information (PI) and any further risk minimisation measures (RMMs) deemed necessary.

4.3.4. Leflunomide – ARAVA (CAP) - EMEA/H/C/000235/SDA/057, LEFLUNOMIDE MEDAC (CAP) - EMEA/H/C/001227/SDA/012, LEFLUNOMIDE WINTHROP (CAP) - EMEA/H/C/001129/SDA/025, NAPs; teriflunomide – AUBAGIO (CAP) - EMEA/H/C/002514/SDA/003

Applicant: Sanofi-aventis Deutschland GmbH (Arava, Leflunomide Winthrop), Sanofi-Aventis Groupe (Aubagio); Medac Gesellschaft fur klinische Spezialpraparate GmbH (Leflunomide

Medac)

PRAC Rapporteur: Sabine Straus

Scope: Signal of falsely decreased ionised calcium levels

EPITT 18787 – Follow up to December 2016

Background

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

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAHs of teriflunomide- and leflunomide-containing products should submit a variation to include a warning on interference with determination of ionised calcium levels.

Summary of recommendation(s)

- The MAH for teriflunomide- and leflunomide-containing products should submit to EMA or to the national competent authorities of the Member States as applicable, within 60 days, a variation for amending the product information[4].
- The PRAC also considered that National Competent Authorities in Member States responsible for vigilance of in vitro diagnostics should be informed about this safety signal so that they can consider pertinent actions and information of relevant parties accordingly.

For the full PRAC recommendation, see EMA/PRAC/221998/2017 published on 21/04/2017 on the EMA website.

4.3.5. Selexipag - UPTRAVI (CAP) – EMEA/H/C/003774/SDA/004

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams

Scope: Signal of fatal cases in patients with pulmonary arterial hypertension (PAH)

EPITT 18833 – Follow up to February 2017

Background

The MAH replied to the request for information on the signal of fatal cases in patients with pulmonary arterial hypertension (PAH) and the responses were assessed by the Rapporteur. For background information, see PRAC minutes February 2017.

Discussion

Having considered the available evidence from the five index case reports in France, clinical trials, literature, post-marketing data, as well as the analyses submitted by the MAH, the PRAC agreed that the currently available data did not warrant any regulatory action at present and therefore the current assessment procedure should be closed. In particular, the PRAC noted that trend analysis of data from clinical trials and post-marketing show similar

[4] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

mortality rates, causes of death and patterns in time to death for selexipag and other PAH treatments.

The PRAC concluded that whilst limitations of the data mean that a possible signal cannot be entirely excluded, the available data also do not provide evidence to further strengthen the signal. However, it was recommended that this issue should be kept under close review and emerging data from ongoing and planned studies will be carefully evaluated as they become available.

Summary of recommendation(s)

- The issue of fatal cases reported in patients with PAH should be kept under close review and emerging data from ongoing and planned studies will be carefully evaluated as they become available.
- In future PSURs the MAH of Uptravi (selexipag) should include a discussion of all sources of mortality data together, including from the ongoing GRIPHON-OL[5] study, the planned PASS EXPOSURE[6], registries, post-marketing spontaneous reports and published literature, including in particular the physician's causality statement and to what extent death is considered attributable to underlying disease. In the next PSUR, the MAH should provide a cumulative review of all post-marketing fatal cases according to concomitant use of inhibitors of CYP2C8[7] and possible role in fatal cases. Moreover, data from PASS EXPOSURE should be provided in each PSUR submitted on a 6-monthly frequency.

4.3.6. Temozolomide - TEMODAL (CAP) - EMEA/H/C/000229/SDA/041; NAPs

Applicant: Merck Sharp & Dohme Limited; various

PRAC Rapporteur: Martin Huber

Scope: Signal of meningoencephalitis herpetic

EPITT 18785 – Follow up to December 2016

Background

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

Discussion

Having considered the available evidence from the evaluation of the data submitted by the MAHs as well as in EudraVigilance and in the literature, the PRAC agreed that the MAHs of temozolomide-containing products should submit a variation to include a warning on meningoencephalitis herpetic and to add meningoencephalitis herpetic (including cases with fatal outcome) as an undesirable effect with an uncommon frequency.

Summary of recommendation(s)

[5] Long term single aim open cohort study to assess the safety and tolerability of selexipag in patients with pulmonary hypertension
[6] European observational study of selexipag in real-life, an observational cohort study of pulmonary arterial hypertension (PAH) patients exposed and unexposed to selexipag in routine clinical practice (AC-065A401)
[7] Cytochrome P450 2C8

- The MAHs for temozolomide-containing products should submit to EMA or to the national competent authorities of the Member States as applicable, within 60 days, a variation for amending the product information[8].

For the full PRAC recommendation, see EMA/PRAC/221998/2017 published on 21/04/2017 on the EMA website.

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 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).

5.1.1. Adalimumab – EMEA/H/C/004279

Scope: Treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

5.1.2. Atezolizumab - EMEA/H/C/004143

Scope: Treatment of locally advanced or metastatic urothelial carcinoma and non-small cell lung carcinoma (NSCLC)

5.1.3. Brodalumab – EMEA/H/C/003959

Scope: Treatment of moderate to severe plaque psoriasis

For further background, see PRAC minutes September 2016, PRAC minutes October 2016 and PRAC minutes March 2017.

5.1.4. Ciclosporin - EMEA/H/C/004411, Orphan

Applicant: Santen Oy

Scope, accelerated assessment: Treatment of severe vernal keratoconjunctivitis (VKC)

5.1.5. Cladribine - EMEA/H/C/004230

Scope: Treatment of highly active relapsing-remitting multiple sclerosis (MS)

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

5.1.6. Glecaprevir, pibrentasvir - EMEA/H/C/004430

Scope, accelerated assessment: Treatment of chronic hepatitis C virus (HCV) infection in adults

5.1.7. Insulin lispro - EMEA/H/C/004303

Scope: Treatment of diabetes mellitus

5.1.8. Ribociclib - EMEA/H/C/004213

Scope: Treatment of breast cancer

5.1.9. Sofosbuvir, velpatasvir, voxilaprevir - EMEA/H/C/004350

Scope, accelerated assessment: Treatment of chronic hepatitis C virus in adults (HCV) infection in adults

5.1.10. Telotristat ethyl - EMEA/H/C/003937, Orphan

Applicant: Ipsen Pharma

Scope: Treatment of carcinoid syndrome

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 Annex I 15.3.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/201609

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Bedaquiline is a diarylquinoline indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be achieved for reasons of resistance or tolerability.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sirturo, a centrally authorised medicine containing bedaquiline, 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 Sirturo (bedaquiline) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information about the increase in bedaquiline exposure in pharmacokinetic (PK) studies in subjects treated with bedaquiline as part of therapy for drug–resistant tuberculosis together with lopanivir/ritonavir-based antiretroviral therapy. Therefore the current terms of the marketing authorisation(s) should be varied[9]. Of note, no change in bedaquiline dosing is recommended in case of co-treatment with lopinavir/ritonavir or other ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors.

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. Daptomycin - CUBICIN (CAP) - PSUSA/00000931/201609

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Daptomycin is a cyclic lipopeptide that is active against Gram positive bacteria indicated for the treatment of complicated skin and soft-tissue infections (cSSTI), right-sided infective endocarditis (RIE) due to Staphylococcus aureus and Staphylococcus aureus bacteraemia (SAB) when associated with cSSTI or RIE.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cubicin, a centrally authorised medicine containing daptomycin, 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 Cubicin (daptomycin) in the approved indication(s) remains unchanged.

[9] Update of SmPC section 4.5. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include 'organising pneumonia' as a recognised presentation of eosinophilic pneumonia. Therefore the current terms of the marketing authorisation(s) should be varied[10].
- In the next PSUR, the MAH should update the indications mentioned in the executive summary and the introduction, to include all authorised indications for paediatric populations. The MAH should also provide a cumulative review of thrombocytopenia including any reports of thrombocytopenia or platelet count decreased reported in the next PSUR (DLP: 11/09/2017) and comment on the need to include routine monitoring for bone marrow toxicity in the product information. In addition, the MAH should comment on the need to add a warning regarding the monitoring of liver transaminases, as part of the review of the potential risk of severe hepatotoxicity.

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

6.1.3. Denosumab[11] - PROLIA (CAP) - PSUSA/00000954/201609

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human monoclonal antibody indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In addition, it is indicated for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prolia, a centrally authorised medicine containing denosumab, 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 Prolia (denosumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on osteonecrosis of the external auditory canal and its possible risk factors. Osteonecrosis of the external auditory canal should also be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- The MAH should submit to EMA, within 180 days, the next annual report of the ongoing PASS study 20090522, entitled 'denosumab global safety assessment among women

[10] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[11] Treatment of osteoporosis and for bone loss associated with hormone ablation in prostate cancer indications only
[12] 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

with postmenopausal osteoporosis (PMO) and men with osteoporosis in multiple observational databases'.

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. Denosumab[13] - XGEVA (CAP) - PSUSA/00009119/201609

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human monoclonal antibody indicated in the prevention of skeletal related events in adults with bone metastases from solid tumours under certain conditions and in the treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xgeva, a centrally authorised medicine containing denosumab, 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 Xgeva (denosumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on osteonecrosis of the external auditory canal and its possible risk factors. Osteonecrosis of the external auditory canal should also be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- The MAH should submit to EMA, within 180 days, the next annual report of the ongoing osteonecrosis of the jaw (ONJ) case registry 20101102.
- In the next PSUR, the MAH should provide a discussion on the potential of causal relationship between denosumab treatment and new primary malignancy as well as a delay in diagnosis of primary malignancy in giant cell tumour of bone (PMGCTB).

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.

[13] Treatment of skeletal related events associated with bone metastases and of giant cell tumour of bone indications only
[14] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.5. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201609

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Dulaglutide is an acting glucagon-like peptide (GLP)-1 receptor agonist indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy and add-on combination therapy, under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Trulicity, a centrally authorised medicine containing dulaglutide, 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 Trulicity (dulaglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hypersensitivity' as an undesirable effect with an uncommon frequency as well as 'anaphylactic reaction' and 'angioedema' with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- The MAH should be requested to update the RMP accordingly for 'hypersensitivity, including anaphylactic reactions' which should be included as an important identified risk, at the next regulatory opportunity.

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

6.1.6. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201609

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Eftrenonacog alfa is a factor IX, a vitamin-K dependent coagulation factor indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Alprolix (eftrenonacog alfa) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include that the occurrence of factor IX (FIX) inhibitor development and hypersensitivity have been observed in post-marketing experience. Therefore the current terms of the marketing authorisation(s) should be varied[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.

6.1.7. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201609

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

Background

Guanfacine is a selective alpha2A-adrenergic receptor agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Intuniv, a centrally authorised medicine containing guanfacine, 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 Intuniv (guanfacine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'erectile dysfunction' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide the rationale of using guanfacine through compassionate use in countries where the product was not launched yet by supplying it from countries where it was already marketed. In addition, the MAH should consider the adverse drug reaction 'pancreatitis' as a safety issue and all new cases or new evidence should be described. Moreover, the MAH should submit a cumulative review and a critical discussion of suicidal ideation/behaviour cases. Finally, the MAH should provide a cumulative review of QT prolongation cases using the MedDRA SMQ[18] 'torsade de pointes/QT prolongation', also submitting information on the cases observed in clinical trials, and consider accordingly the need to update the product information and/or RMP if appropriate.

[16] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[17] 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
[18] Medical dictionary for regulatory activities - standardised MedDRA queries (SMQ)

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. Idebenone[19] - RAXONE (CAP) - PSUSA/00010412/201609

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

Idebenone is a short-chain benzoquinone indicated for the treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy (LHON).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Raxone, a centrally authorised medicine containing idebenone, 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 Raxone (idebenone) 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 monitor 'blurred vision' and 'atrial fibrillation', as well as discuss 'hepatobiliary disorders' in order to gather more post-marketing data.

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. Infliximab[20] - REMICADE (CAP) - PSUSA/00010231/201608

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Infliximab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis under certain conditions.

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

[19] Centrally authorised product(s) only
[20] Biosimilars excluded

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Remicade (infliximab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a summary of available data on response to common vaccines, including pneumococcal vaccines, in patients on Remicade (infliximab) for the different approved indications and discuss the need to update the product information accordingly.
- In the next PSUR, the MAH should review the biological plausibility for progressive multifocal leukoencephalopathy (PML) to occur in immunosuppressed patients such as those treated with infliximab, as cases continue to be reported in infliximab-exposed subjects. In addition, the MAH should also provide a comprehensive summary of the number of cumulative cases of glomerulonephritis as well as the number of cases reported according to subtype, along with information on confounding factors, positive dechallenge, rechallenge and other information important for assessment of causality. Finally, the MAH should provide cumulative reviews of the safety issues 'antiphospholipid syndrome' and 'pancreatic carcinoma'. Regarding the antiphospholipid syndrome, the MAH should describe for each of the reported cases whether they were associated with other positive autoantibodies than antiphospholipid antibodies.

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

6.1.10. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201609

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naltrexone is an opioid antagonist and bupropion an aminoketone derivative. The combination is indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone and bupropion, 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 Mysimba (naltrexone, bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the warning on hepatotoxicity and update the warning on suicidal behaviour to indicate that the risk of suicidality events does not predominantly concern younger patients below the age of 25

years, but patients above the age of 40 years. In addition, hepatotoxicity should be added as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].

- In the next PSUR, the MAH should provide an analysis of the cumulative clinical trial data on adverse events in the elderly. In addition, the MAH should submit an evaluation of serotonin syndrome. Furthermore, regarding the possibility of 'angioedema' as an adverse drug reaction of the combination and not only of bupropion, the MAH should present an analysis including data reviewed and a discussion. Finally, the MAH should review and analyse all the cases of seizure from clinical trials.

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. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201609

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor indicated, as monotherapy, for the treatment of advanced (unresectable or metastatic) melanoma in adults as well as for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keytruda, a centrally authorised medicine containing pembrolizumab, 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 Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include sarcoidosis as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH should discuss thoroughly the topics of 'pneumonia' and 'Vogt-Koyanagi-Harada syndrome' associated with pembrolizumab, and consequently the need for any (additional) risk minimisation activities, including any updates to the product information with a proposal for changes if deemed necessary. In addition, the MAH should provide an updated cumulative review of 'encephalitis'.

[21] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[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

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.

6.1.12. Regorafenib - STIVARGA (CAP) - PSUSA/00010133/201609

Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

Background

Regorafenib is a protein kinase inhibitor indicated for the treatment of metastatic colorectal cancer (CRC) and for the treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Stivarga, a centrally authorised medicine containing regorafenib, 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 Stivarga (regorafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'dehydration' as an undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a clarification on 'exposure-adjusted' calculations for clinical trial data. Moreover, the MAH should provide a detailed review of all new cases of peripheral neuropathy, with the aim of proposing appropriate product information wording if applicable.

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.

6.1.13. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/201609

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Rivaroxaban is a highly selective direct factor Xa inhibitor indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, for the prevention of venous thromboembolism (VTE) in adult

[23] 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

patients undergoing elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for the prevention of recurrent DVT and PE in adults, and for the prevention of stroke and systemic embolism in adult patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xarelto, a centrally authorised medicine containing rivaroxaban, 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 Xarelto (rivaroxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding Stevens-Johnson syndrome/toxic epidermal necrolysis and to add 'Stevens-Johnson syndrome/toxic epidermal necrolysis' as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAH should provide a cumulative review of hearing disorders, drug reactions with eosinophilia and systemic syndromes (DRESS) and pancreatitis reported with rivaroxaban, as well as a cumulative review of arthralgia, back pain, musculoskeletal pain and myalgia. In addition, the MAH should include a review of any new cases of agranulocytosis and alopecia. Furthermore, the MAH should include a cumulative assessment of cases in which rivaroxaban was administered together with fluconazole, and follow and report on the topics of renal failure (not directly caused by bleeding), dyspnoea, and paraesthesia and hypoesthesia, especially if new cases emerge. Finally, The MAH should propose an update of the product information and/or the RMP if considered relevant.

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.

6.1.14. Telbivudine - SEBIVO (CAP) - PSUSA/00002880/201608

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Telbivudine is a thymidine nucleoside analogue indicated for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sebivo, a centrally authorised medicine containing telbivudine, 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 Sebivo (telbivudine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reinforce the current warning on lactic acidosis and delete the reference to a secondary event often associated with serious conditions for the undesirable effect 'lactic acidosis'. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- The MAH should submit to EMA, within 60 days, an updated RMP to re-categorise the risk of 'lactic acidosis' from an important potential risk to an important identified risk including a draft targeted questionnaire for fatal cases.
- In the next PSUR, the MAH should provide a thorough presentation of fatal cases with a detailed description, including narratives and an analysis of causes of deaths.

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.

6.1.15. Teriflunomide - AUBAGIO (CAP) - PSUSA/00010135/201609 (with RMP)

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Teriflunomide is a selective immunosuppressant indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aubagio, a centrally authorised medicine containing teriflunomide, 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 Aubagio (teriflunomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the existing warning on respiratory reactions in relation to interstitial lung disease (ILD), to include the undesirable effects events ILD, acute hepatitis, asthenia and nail disorders with an unknown frequency and to consider alanine aminotransferase (ALT) increase, gamma-glutamyl transferase (GGT) increase and aspartate aminotransferase increase under

[25] 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

'hepatobiliary disorders'. Therefore the current terms of the marketing authorisation(s) should be varied[26].

- In the next PSUR, the MAH should discuss the need to update the product information in relation to nail disorders based on the cumulative evidence and propose appropriate wording if deemed necessary. Moreover, the signal for tachycardia and cardiac rhythm disorders should remain ongoing and the MAH should report relevant new safety information through the signal management process. In addition, the MAH should perform a cumulative review of all cases of colitis from post-marketing reports, clinical studies and scientific publications and propose a product information update 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.

6.1.16. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/201609

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

Trabectedin is an antineoplastic agent indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents, and in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yondelis, a centrally authorised medicine containing trabectedin, 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 Yondelis (trabectedin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on capillary leak syndrome (CLS), as well as CLS as an undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].

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

[26] Update of SmPC 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
[27] 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

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

6.2.1. Anagrelide - XAGRID (CAP); NAP - PSUSA/00000208/201609

Applicant(s): Shire Pharmaceutical Contracts Ltd. (Xagrid), various

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

Background

Anagrelide is an inhibitor of the cyclic adenosine monophosphate (AMP) phosphodiesterase III indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xagrid, a centrally authorised medicine containing anagrelide, as well as nationally authorised medicines containing anagrelide, 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 anagrelide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'pulmonary hypertension' and to change the frequency of the undesirable effect 'pulmonary hypertension' to an uncommon frequency. Therefore the current terms of the marketing authorisations should be varied[28].
- In the next PSUR, the MAHs should ensure close monitoring of cases of posterior reversible encephalopathy syndrome (PRES), and discuss any new cases.

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

6.2.2. Zoledronic acid[29] - ZOLEDRONIC ACID HOSPIRA (CAP); ZOLEDRONIC ACID MEDAC (CAP); ZOMETA (CAP); NAP - PSUSA/00003149/201608

Applicant(s): Hospira UK Limited (Zoledronic acid Hospira), Medac Gesellschaft fur klinische Spezialpraparate GmbH (Zoledronic acid Medac), Novartis Europharm Ltd (Zometa), various

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

[29] Treatment of cancer and fractures indication(s) only

Background

Zoledronic acid is a bisphosphonate indicated for the prevention of skeletal related events in adult patients with advanced malignancies involving bone and for the treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zoledronic acid Hospira, Zoledronic acid Medac and Zometa, centrally authorised medicines containing zoledronic acid, as well as nationally authorised medicines containing zoledronic acid, 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 zoledronic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on osteonecrosis of other anatomical sites and also to add osteonecrosis of other anatomical sites including femur and hip as an undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisations should be varied[30].
- In the next PSUR, the MAH Novartis should include a systematic review of the frequencies of 'uveitis', 'episcleritis' and similar eye disorders following zoledronic acid use. All MAHs should closely follow-up the signal of fractures related to osteonecrosis other than the jaw and external auditory canal, and report any new cases.

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

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

See also Annex I 16.3.

6.3.1. Finasteride (NAP) - PSUSA/00001392/201608

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of type II 5 alpha-reductase, an intracellular enzyme that metabolises the androgen testosterone to dihydrotestosterone (DHT). It is indicated for the treatment of, and control of, benign prostatic hyperplasia (BPH) and for the prevention of urologic events under certain

[30] 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

conditions, and for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

In February 2017, the PRAC gave advice to Member States, following a PRAC consultation on a variation procedure for Propecia, Pilus (finasteride) (SE/H/xxx/WS/139) which explored the possible causal relationship between finasteride 1 mg for the treatment of alopecia and the risk of depression. For further background, see PRAC minutes February 2017.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing finasteride, 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 nationally authorised finasteride-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) of medicinal products containing 1 mg of the active substance finasteride in the male pattern hair loss (MPHL) indication should be maintained.
- Nevertheless, the product information of medicinal products containing 5 mg finasteride for the benign prostate hyperplasia (BPH) indication should be updated to include a warning on depression and suicidal ideation. Therefore the current terms of the marketing authorisations should be varied[31].
- In the next PSUR, the MAHs (for both MPHL and BPH indications) should closely monitor events of suicide, suicidality and self-injury and any new cases for both finasteride 5 mg and 1 mg should be reported by the MAHs including full case narratives as well as a causality assessment. The MAHs should also closely monitor events of penile size reduced and testicular atrophy and any new cases should be discussed by the MAHs. In addition, the MAHs should provide a cumulative review of anxiety. The MAHs for the MPHL indication only should provide a cumulative review of reports describing sexual dysfunction-related events reported in conjunction with psychiatric disorder events with a discussion on the need to update the product information. Finally, the MAHs for MPHL indication only should provide a cumulative review of psychiatric disorders persisting after finasteride discontinuation and comment on the need to update the product information.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

[31] 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

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[32]

See also Annex I 17.1.

7.1.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSA/S/0016

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: MAH's request for a 2-months extension to respond to the amended PASS protocol (amendment 1, version 3.0) for study CC-5013-MDS-012: a retrospective drug-utilisation study to describe patterns of Revlimid use (from II/56 (extension of indication)

Background

Revlimid is a centrally authorised medicine containing lenalidomide, an anti-neoplastic, anti-angiogenic and pro-erythropoietic immunomodulator. It is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for a transplant, and indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

In April 2014, the PRAC adopted the protocol for a non-interventional PASS (study CC-5013-MDS-012) designed as a retrospective drug-utilisation study to describe patterns of Revlimid use. Further to the MAH submission of a substantial protocol amendment (updated protocol Amendment 1, version 3.0), the PRAC objected to the amended protocol in March 2017, as the Committee considered that the design of the study did not fulfil the study objectives. The PRAC therefore recommended a revision of the protocol in line with the study objectives finally imposed by the PRAC and submission of a revised PASS protocol within 60 days to the EMA. For further background, see PRAC minutes April 2014 and PRAC March 2017 minutes. The MAH requested on 24 March 2017 a two-month extension of the revised PASS protocol submission deadline.

Endorsement / Refusal of the protocol

- The PRAC agreed to the MAH request of a 60 days extension of the revised PASS protocol submission deadline.
- The MAH should submit a revised PASS protocol within 90 days to the EMA.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[33]

See also Annex I 17.2.

[32] In accordance with Article 107n of Directive 2001/83/EC
[33] 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

7.2.1. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/MEA 001.2

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 001.1: revised protocol for a non-interventional non-imposed PASS (AC-065A401): an observational cohort study of pulmonary arterial hypertension (PAH) patients exposed and unexposed to selexipag in routine clinical practice, as per the request for supplementary information (RSI) adopted in February 2017

Background

Uptravi is a centrally authorised medicine containing selexipag indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO 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.

As part of the RMP for Uptravi (selexipag), the MAH was required to conduct a category 3 PASS entitled 'an observational cohort study of pulmonary arterial hypertension (PAH) patients exposed and unexposed to selexipag in routine clinical practice' (EXPOSURE (AC-065A401)). The study aims to further characterise the safety profile of Uptravi and to describe clinical characteristics and outcomes of patients newly treated with Uptravi in the European post-marketing setting. Further to the previous advice adopted by PRAC in February 2017, the MAH submitted a revised protocol (version 4) which was assessed by the Rapporteur. For further background, see PRAC minutes February 2017.

Summary of advice

- The study protocol for the PASS EXPOSURE (AC-065A401), version 4 as well as its German version 4.DEU.A for Uptravi (selexipag) are considered acceptable.

7.3. Results of PASS imposed in the marketing authorisation(s)[34]

7.3.1. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0005.1

Applicant: Bayer Pharma AG (Diane 35); various

PRAC Rapporteur: Menno van der Elst

Scope: Addendum to final study results, with additional French data on the drug utilisation study (DUS) (survey) designed to characterize the prescribing behaviours for cyproterone acetate/ethinylestradiol (CPA/EE) in five European countries: Austria, Czech Republic, France, the Netherlands and Spain

Background

In line with the conclusions of a procedure under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), the MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices for these medicinal products during typical clinical use in

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

representative groups of prescribers, and to assess the main reasons for prescription. The protocol for this study was assessed and endorsed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. Further to the review by PRAC of the PASS study results and recommendations issued on the marketing authorisations, the PRAC reviewed the addendum to the final study results, with additional French data on the DUS submitted on 1 February 2017. For background information, see PRAC minutes April 2014, PRAC minutes September 2014, PRAC minutes October 2014, PRAC minutes December 2014, PRAC minutes April 2015, PRAC minutes April 2016, PRAC minutes June 2016 and PRAC minutes December 2016.

Summary of advice

- Based on the review of the non-interventional imposed PASS addendum to the final study report (version ZEG2016), dated 21 December 2016, the PRAC considered the new data set for France in line with the data in the main report. The addendum did not have any impact on the results and conclusions of the main procedure (EMEA/H/N/PSR/J/0005), as well as the PRAC recommendation issued on the marketing authorisations.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[35]

See Annex I 17.4.

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

See Annex I 17.5.

7.6. Others

See also Annex I 17.6.

7.6.1. Valproate (NAP) - EMEA/H/N/PSI/J/0001

Applicant(s): Sanofi; various

PRAC Rapporteur: Sabine Straus

Scope: Submission of the first interim study report of a non-interventional imposed PASS, designed to assess the effectiveness of risk minimisation measures in the outpatient setting, including the 3-year data collected for the pre-implementation period in 4 out of 5 countries (France, Germany, Spain, Sweden and United Kingdom) versus the 6-month data collected for the post-implementation period in all of the five EU selected countries, and submission of the final study report of the Joint PASS survey among healthcare professionals (HCPs) to assess their knowledge and attitudes on the prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom

[35] 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

Background

Valproic acid is an acidic organic compound, and valproate and related salts and esters are indicated for the treatment of generalised, partial or other types of epilepsy, and for the treatment of manic episodes in bipolar disorder under certain conditions. Valproate is also indicated in some Member States to prevent migraine headaches.

In October 2014 the PRAC adopted a recommendation for consideration by the CMDh for the referral under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate and related substances strengthening the restrictions on the use of valproate in female patients. In addition, to improve the safety information and awareness of both female patients and HCPs about the risks of valproate exposure during pregnancy, the PRAC recommended providing educational materials (EM) to HCPs. As part of the risk minimisation measures (RMMs), the PRAC requested the MAHs of valproate to perform in parallel a drug utilisation study (DUS) to assess the effectiveness of the measures and to further characterise the prescribing patterns for valproate with a pre- and post-implementation analysis and assessment, in more than one Member State, and a PASS survey in five European countries to assess the effectiveness of the direct healthcare professional communication (DHPC) and EM, part of the measures implemented, as well as whether physicians received the updated prescribing conditions and safety warnings/information, understood and follow them when prescribing valproate. For further background, see PRAC minutes January 2016, PRAC minutes July 2015 and PRAC minutes September 2015.

A revised protocol for a post-authorisation safety study (DUS) to assess the effectiveness of the RMMs and to further characterise the prescribing patterns for valproate was submitted to the PRAC by a consortium of MAHs in accordance with conditions to the marketing authorisations included in the EC decision Annex IV for the referral under Article 31 of Directive 2001/83/EC (EMA/612389/2014) for valproate-containing medicine and was endorsed by the PRAC in January 2016 (see PRAC minutes January 2016).

The consortium of MAHs submitted interim results (the first interim report) of this PASS. In addition, the final report of the joint PASS survey among HCPs to assess their knowledge and attitudes on prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom was also submitted for assessment.

Summary of advice

- The PRAC discussed the interim results of the DUS valproate and related substances including the results for four of the five EU countries (i.e. France, Germany, Spain and UK) which compared the prescription of valproate and related substances during the 21 month period before the referral on valproate-containing medicines was announced (so called pre-implementation period) with the prescription data from the period after the DHPC and educational materials were distributed (post-implementation period, which is 6 months in this first interim report). The PRAC noted a preliminary conclusion based on the data presented in the first interim report of the DUS, indicating that the prescribing pattern of valproate regarding use in women of childbearing potential did not really change when comparing the pre-implementation period (21 months) with the post-implementation period (6 months only). However, no firm conclusions could be drawn yet since only a limited period of 6 months was included in the post-implementation period and data from Sweden were missing. The PRAC considered that additional analyses are required and the MAH Consortium should perform further evaluation on current available data and further discuss how to improve the findings.

- The PRAC also discussed the final study report of the joint PASS survey among HCPs to assess their knowledge and attitudes on prescribing conditions of valproate in France, Germany, Spain, Sweden and United Kingdom. The PRAC noted that these preliminary results indicate that HCPs may have limited knowledge regarding the need to consider alternative treatments if a woman becomes or plans to become pregnant during valproate treatment and the need to regularly review the need for treatment and re-assess the balance of the benefits and risks for women and also for girls reaching puberty who are taking valproate. The PRAC noted room for improvement in the knowledge and attitudes of the HCPs regarding the need to conduct continuous routine re-evaluation of the therapeutic place of valproate in women of child bearing potential (WCBP) in view of the possibility of changing benefit risk balance in female patients during different age stages. The PRAC considered that additional analyses were required and the MAH Consortium should discuss on how to improve the findings.
- Based on the PRAC Rapporteur review of the PASS first interim report of the DUS and the final study report of the Survey, the PRAC considered that the risk-benefit balance of valproate containing medicinal products concerned by the PASS interim report of the DUS and the final study report of the Survey was subject to a request for supplementary information to be addressed within 30 days.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

10.3.1. Desloratadine - AERIUS (CAP); AZOMYR (CAP); DASSELTA (CAP); DESLORATADINE ACTAVIS (CAP); DESLORATADINE RATIOPHARM (CAP); DESLORATADINE TEVA (CAP); NEOCLARITYN (CAP); NAP – EMEA/H/A-5(3)/1431

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

PRAC Rapporteur: Jean-Michel Dogne; PRAC Co-rapporteur: Jan Neuhauser

Scope: PRAC consultation on an ongoing CHMP review under Article 5(3) of Regulation (EC) No 726/2004 evaluating the possible switch of the prescription status of nationally-authorised desloratadine-containing products from 'medicinal products subject to prescription' to 'medicinal products not subject to prescription' (also known as over-the-counter or OTC)

Background

Desloratadine is the active metabolite of loratadine and a non-sedating, long-acting histamine antagonist indicated for the relief of symptoms associated with allergic rhinitis and urticaria in adults, adolescents and children over the age of one year (depending on the formulation and the strength). On 16 December 2015, BfArM requested a scientific opinion by the CHMP under Art 5(3) of Regulation (EC) No 726/2004, on whether desloratadine-containing products should be switched to non-prescription status. In February 2017, the CHMP requested advice from the PRAC on this procedure, considering that the criteria driving the classification as prescription versus non-prescription pertain mainly to safety aspects. For further background, see CHMP minutes December 2015 and CHMP minutes February 2016.

Summary of advice

- Based on the available data, the PRAC considered the safety profile of desloratadine assessed by CHMP and highlighted the PRAC recommendation adopted during the PRAC March 2017 meeting on the desloratadine PSUSA procedure (see PRAC minutes March 2017). The PRAC also noted that the safety profile described in the summary of product characteristics (SmPC) of desloratadine-containing products differs from that described in the SmPC of loratadine products, but the inherent limitations of clinical trials and spontaneous reporting data preclude firm conclusions in this regard. Of note, there is an ongoing PASS which is expected to clarify some existing uncertainties in the safety profile of desloratadine. Based on the information currently available, it was not considered possible to draw a conclusion on whether differences in prescription status impact the risk associated with each product.

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.

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

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Best Practice guide on efficiency – implementation quantitative goals – Q1 2017 statistics

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

Following the adoption at PRAC of the best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016) and of the implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016), the PRAC was updated at the organisational matters teleconference held on 20 April 2017 on quantitative measures collected for the first 2017 quarter of PRAC meetings as well as cumulatively since July 2016. See previous updates, PRAC minutes November 2016 and PRAC minutes February 2017.

12.2. Coordination with EMA Scientific Committees or CMDh

None

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

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

As a follow-up to the last PRAC discussions on the exercise to revise the 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' (EMEA/149995/2008) (see PRAC minutes January 2016 and PRAC minutes April 2016, PRAC minutes July 2016 and PRAC minutes February 2017), the PRAC was presented by the EMA Secretariat with an updated version of the guideline for discussion with a view to hold a follow-up discussion and possibly adopt the final guidance in July 2017 for public consultation. The PRAC commented that the principles of GVP module V on 'risk management system' would apply.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

12.5.1. Direct oral anticoagulants (DOAC) EMA-funded study - update on study protocol and international collaboration

Following the presentation by the EMA Secretariat to the PRAC in February 2016 of a proposal for an EMA-funded non-interventional study to assess the safety and effectiveness of direct oral anticoagulants (DOAC) and warfarin in EU patients with non-valvular atrial fibrillation, with particular focus on high-risk patients, and the finalisation of the protocol in January 2017, the PRAC was updated on the study design and implementation of the same protocol (selected objectives) in Canadian databases by the CNODES consortium with funding from Health Canada. For further background, see PRAC minutes February 2016.

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

12.6.1. Patient registry initiative - update and organisation of a workshop on cystic fibrosis (CF) on 14 June 2017 and a workshop on multiple-sclerosis (MS) on 7 July 2017

Patient registries are organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, that is followed over time. The initiative for patient registries, launched in September 2015, explores ways of expanding the use of patient registries by introducing and supporting a more systematic and standardised approach to their contribution to the benefit-risk evaluation of medicines within the European Economic Area (EEA). To better understand the challenges and barriers to collaboration between stakeholders, EMA held a stakeholder workshop in October 2016 and published a workshop report in February 2017 including some recommendations. The EMA secretariat updated the PRAC on the workshop recommendations to organise two workshops, one on cystic fibrosis (CF) and one on multiple-sclerosis (MS), with the objective to agree on implementable recommendations on core data elements to be collected, protocols, consents, governance supporting registry interoperability and on the workplan for the further development and finalisation of recommendations to be adopted by registry holders and MAHs/applicants.

12.7. PRAC work plan

None

12.8. Planning and reporting

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

The EMA secretariat presented, at the organisational matters teleconference held on 20 April 2017, quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, where available, and per NCA for the upcoming months.

12.8.2. Marketing authorisation applications (MAA) expected for 2017 – Q1 2017 update

The EMA Secretariat presented, at the organisational matters teleconference held on 20 April 2017, for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). See previous updates, PRAC Minutes October 2016 and PRAC Minutes January 2017.

12.8.3. PRAC workload statistics - Q1 2017

The EMA secretariat presented, at the organisational matters teleconference held on 20 April 2017, quarterly figures to estimate the evolution of the workload of the PRAC, by reflecting the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, PRAC minutes February 2017.

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)

None

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 April 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 April 2017, the updated EURD list was adopted by the CHMP and CMDh at their April 2017 meetings and published on the EMA website on 12/05/2017, 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 April 2017 SMART Working Group (SMART WG) work stream WS1. The WG WS1 discussed the issue 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. A possible solution might be a list of publications (likely in the form of a spreadsheet) already reviewed, together with a comment on their relevance and the need for any regulatory actions. This could then be shared with the EU network. The WG WS1 was also updated on the revised list of signal worksharing and the frequency of monitoring electronic reaction monitoring reports (eRMR). An issue was raised regarding the peaks of workload due to the production of all eRMRs in the same month and EMA will consider amending the month of production to avoid three-monthly and six-monthly eRMRs coinciding in the same month. In addition, the WG WS1 discussed the potentially high number of MAH-validated signals when access to EudraVigilance is extended to MAHs and possible solutions.

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

PRAC lead: Sabine Straus

The PRAC discussed possible solutions for the handling of MAH signals following increased EudraVigilance access by MAHs in order to prevent duplicative work. A follow-up discussion will be held at PRAC in May 2017.

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 – impact on pharmacovigilance performance

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 mandated by the legislation to analyse experience with the black triangle in the context of pharmacovigilance performance in the EEA countries. For further background, see PRAC minutes February 2017. The PRAC reviewed the preliminary study protocol and provided comments to the EMA Secretariat that were discussed during the meeting and at the organisational matters teleconference held on 20 April 2017. The collection of data and analysis will start in May 2017 for a report expected by end of 2017/beginning of 2018.

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

12.13. EudraVigilance database

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

Following the last discussion on the EudraVigilance (EV) auditable requirement project (see PRAC minutes June 2016 and PRAC minutes January 2017), the EMA secretariat provided the PRAC with a status report on the PRAC audit recommendation decision process and the independent final audit report, including the key findings of the audit. Points for clarification were raised by PRAC. The EMA secretariat agreed to provide the requested information, as well as a 're-routing test plan' including a declaration of best efforts in advance of the May 2017 PRAC meeting when the Committee will issue a recommendation on the independent final audit report of EudraVigilance.

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

12.14.3. Strategy on measuring the impact of pharmacovigilance activities - effectiveness of risk minimisation measures: diclofenac and hydroxyzine impact study protocols

Following the adoption by the PRAC of its 'strategy on measuring the impact of pharmacovigilance activities' (EMA/790863/2015) in January 2016 and of the criteria to prioritise topics for collaborative impact research (EMA/153279/2016) in September 2016 based on the public health importance of the regulatory action, potential impact on clinical practice and delivery of decision-relevant data, the EMA Secretariat presented to the PRAC two impact study protocols: one on diclofenac-containing products and cardiovascular risks to evaluate the impact of the risk minimisation measures following the PRAC recommendation on the review of diclofenac-containing product (systemic formulations) under the under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1344), and the other on hydroxyzine-containing medicines and pro-arrhythmogenic potential to evaluate the impact of the risk minimisation measures following the PRAC recommendation on the review of hydroxyzine-containing medicines (EMEA/H/A-31/1400). For further background, see PRAC minutes July 2016, PRAC minutes September 2016 and PRAC minutes November 2016). Both protocols were endorsed at the organisational matters teleconference held on 20 April 2017.

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

12.15.3. Antiretroviral Pregnancy Registry (APR) – participation of generic[36] medicinal products – follow-up

PRAC lead: Julie Williams

Antiretroviral agents are indicated for the treatment of patients affected by the human immunodeficiency virus (HIV) under certain conditions. The Antiretroviral Pregnancy Registry (APR) is a voluntary patient registry intended to provide ongoing surveillance of outcomes in pregnancies exposed to antiretroviral agents. The requirement for the APR as additional pharmacovigilance is common to innovator antiretroviral (ARV) products regardless of evidence of risk of harm in pregnancy, but this requirement has been applied on an ad hoc basis to generic ARV products. For further background, see PRAC minutes September 2015, PRAC minutes October 2015 and PRAC minutes November 2016.

At the current meeting, the PRAC agreed that MAHs of generic antiretroviral products are not required to routinely participate in the APR. However, a standardised targeted follow-up form to collect data relevant to pregnancy and birth outcomes should be applied across the generic ARV products. Engagement with MAHs of generic ARV products should be conducted

[36] Article 10 (1) of Directive 2001/83/EC

to reinforce that MAHs are still required to conducting pharmacovigilance with regards to pregnancy and pregnancy outcomes, to avoid the perception of lower standards for generics in relation to other post authorisation measures and data gathering. The follow-up pregnancy form will thus be made available on the EMA website and HMA website once finalised and communicated to industry through industry stakeholder platforms.

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

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

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

The PRAC discussed the progress of an ongoing initiative to strengthen assessment of reports of serious cutaneous adverse reactions (SCARs) and to better reflect SCARs in regulatory documents. The initiative is one of the key topics for the PRAC work plan 2017 and takes into consideration the definition of SCARs from a clinical and scientific perspective as a basis to develop a guide for pharmacovigilance assessors, including an assessors' checklist with minimum criteria to consider in relation to SCARs during assessments, as well as a regulatory rationale for including warnings and guidance to patients and prescribers in the product

information. For further background, see PRAC minutes January 2017. At the current meeting, the PRAC discussed the final draft guidance document on SCARs before its adoption planned in Q3/Q4 2017.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[37]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[38].

14.1.1. Gefitinib – IRESSA (CAP)

Applicant (s): AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of recall phenomenon

Action: For adoption of PRAC recommendation

EPITT 18857 – New signal

Lead Member State(s): SE

14.1.2. Meningococcal group B vaccine (rDNA, component, adsorbed) - BEXSERO (CAP)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of arthritis and synovitis

Action: For adoption of PRAC recommendation

EPITT 18764 – New signal

Lead Member State(s): SE

[37] 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

[38] Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.3. Methotrexate – NORDIMET (CAP); NAP

Applicant(s): Nordic Group B.V. (Nordimet), various

PRAC Rapporteur: Martin Huber

Scope: Signal of pulmonary alveolar haemorrhage

Action: For adoption of PRAC recommendation

EPITT 18850 – New signal

Lead Member State(s): DE

14.1.4. Pramipexole – MIRAPEXIN (CAP), SIFROL (CAP), OPRYMEA (CAP), PRAMIPEXOLE TEVA (CAP), PRAMIPEXOLE ACCORD (CAP); NAP

Applicant(s): Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), Krka, d.d., Novo mesto (Oprymea), Teva B.V. (Pramipexole Teva), Accord Healthcare Ltd (Pramipexole Accord); various

PRAC Rapporteur: Doris Stenver

Scope: Signal of dystonia

Action: For adoption of PRAC recommendation

EPITT 18866 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

14.2.1. Azithromycin (NAP); tobramycin[39] – TOBI PODHALER (CAP), VANTOBRA (CAP); NAP

Applicant(s): Novartis Europharm Ltd (Tobi Podhaler), PARI Pharma GmbH (Vantobra); various

PRAC Rapporteur: Sabine Straus

Scope: Signal of possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin

Action: For adoption of PRAC recommendation

EPITT 18855 – New signal

Lead Member State(s): NL, SE

14.2.2. Flucloxacillin (NAP)

Applicant(s): various

PRAC Rapporteur: To be appointed

Scope: Signal of high anion gap metabolic acidosis (HAGMA)

[39] For inhalation use only

Action: For adoption of PRAC recommendation

EPITT 18844 – New signal

Lead Member State(s): PT

14.2.3. Mesalazine (NAP)

Applicant(s): various

PRAC Rapporteur: Patrick Batty

Scope: Signal of risk of photosensitivity reactions

Action: For adoption of PRAC recommendation

EPITT 18869 – New signal

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. Midostaurin - EMEA/H/C/004095, Orphan

Applicant: Novartis Europharm Ltd

Scope: Treatment of mastocytosis and treatment of acute myeloid leukaemia

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. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/II/0033

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 4.2) to reflect the revised protocol for a PASS to capture data on the frequency of resolution and time to resolution of eribulin-induced or aggravated peripheral neuropathy from study E7389-A001-303 (ACCRU: a randomized phase III study of eribulin compared to standard weekly paclitaxel as first- or second-line therapy for locally

recurrent or metastatic breast cancer) to an observational post authorisation, single-arm, prospective multicentre cohort study E7389-M044-504 (IRENE). The submission date of the corresponding study report to EMA remains unchanged and is planned in 2019

15.2.2. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0042

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMP (version 25) following closure and final summary of the exenatide pregnancy registry (a prospective, observational study conducted in the United States that actively collected information on exposure to antidiabetic medication during pregnancy and the associated pregnancy outcomes in patients with type 2 diabetes mellitus (T2DM)). Moreover, the MAH included additional minor updates to the RMP

15.2.3. Human alpha 1-proteinase inhibitor - RESPREEZA (CAP) - EMEA/H/C/002739/II/0013

Applicant: CSL Behring GmbH

PRAC Rapporteur: Eva Segovia

Scope: Update of the RMP (version 3.1) in order to include the final safety data from study CE1226_3001 (an open-label, non-controlled, multicentre, multinational study to evaluate the efficacy and safety of human alpha1-proteinase inhibitor administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha 1-proteinase inhibitor deficiency who completed clinical study CE1226_4001) assessed within EMEA/H/C/002739/II/0002 procedure. Further adjustments in the non-clinical safety specification part are included

15.2.4. Vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/WS1088/0048; JALRA (CAP) - EMEA/H/C/001048/WS1088/0048; XILIARX (CAP) - EMEA/H/C/001051/WS1088/0047 Vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/WS1088/0057; ICANDRA (CAP) - EMEA/H/C/001050/WS1088/0058; ZOMARIST (CAP) EMEA/H/C/001049/WS1088/0058

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of the RMPs (version 14) for Galvus, Jalra, Xiliarx, Eucreas, Icandra and Zomarist in order to reflect the outcome of the recently finalised procedure for metformin-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1432) in order to implement a targeted questionnaire for cases of lactic acidosis

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

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

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

15.3.2. Aliskiren - RASILEZ (CAP) - EMEA/H/C/000780/WS1026/0110; Aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS1026/0080

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of section 5.1 of the SmPC in order to reflect the results of study SPP100F2301 (ATMOSPHERE): a multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of both aliskiren monotherapy and aliskiren/enalapril combination therapy compared to enalapril monotherapy, on morbidity and mortality in patients with chronic heart failure (New York Heart Association (NYHA) Class II-IV). The RMP (version 13) is updated accordingly

15.3.3. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0092

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the use of Avastin in combination with paclitaxel and carboplatin for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated with efficacy and safety information from study GOG-0213 (a phase III randomized controlled clinical trial of carboplatin and paclitaxel (or gemcitabine) alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer). The Package Leaflet and the RMP (version 27) are updated accordingly

15.3.4. Bimatoprost, timolol - GANFORT (CAP) - EMEA/H/C/000668/II/0026

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of section 4.8 of the SmPC to revise and simplify the undesirable effects section as per the PRAC recommendation following PSUSA assessment

(EMEA/H/C/PSUSA/00002961/2015). The Package Leaflet and the RMP (version 3.2) are updated accordingly. In addition, the MAH took the opportunity to update the Product Information in line with the QRD template (version 10.0) to implement the unique identifier 2D bar code and include some editorial corrections

15.3.5. Daptomycin - CUBICIN (CAP) - EMEA/H/C/000637/II/0061

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to extend the *S. aureus* bacteraemia indication to include paediatric patients 1 to 17 years of age. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet, Labelling and the RMP (version 10.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10) and to combine the SmPCs for both strengths (350 and 500 mg)

15.3.6. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0062

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC to update the safety information and reflect the possible occurrence of multiple vertebral fractures (MVF) particularly in patients with a history of vertebral fracture following discontinuation of Prolia treatment. This results from an analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase III pivotal fracture study (study 20030216: evaluation of denosumab in the treatment of postmenopausal osteoporosis FREEDOM (fracture reduction evaluation of denosumab in osteoporosis every 6 months)) or its study extension (study 20060289: open label, single arm, extension study to evaluate the long term safety and sustained efficacy of denosumab in the treatment of postmenopausal osteoporosis) to better understand the incidence of fracture following treatment discontinuation. The Package Leaflet is updated accordingly. The RMP (version 16) is also updated to reflect MVF as a new important risk. In addition, the Product Information is updated in line with the QRD template latest version and corrected to remove typographical errors and implement minor changes in the list of local representatives

15.3.7. Efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/WS1117/0110/G; SUSTIVA (CAP) - EMEA/H/C/000249/WS1117/0139/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped work-sharing variations on: 1) update of sections 4.4, 4.5 and 5.1 of the SmPC in order to add a warning and update the safety information on QTc prolongation based on the final results from study AI266959: an interventional study to determine the concentration-electrocardiographic effects of efavirenz in healthy subjects enriched for

CYP2B6[40] polymorphisms. The Package Leaflet and the RMP (version 8) are updated accordingly; 2) update of sections 4.4 and 4.8 of the SmPC to add catatonia as a psychiatric symptom following an assessment of cases of catatonia reported in the literature and via the United States (US) Food and Drug Administration adverse event reporting system (FAERS)

15.3.8. Efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/WS1133/0121/G; emtricitabine, tenofovir alafenamide - DESCOVY (CAP) –EMEA/H/C/004094/WS1133/0015/G; emtricitabine, rilpivirine, tenofovir disoproxil - EVIPLERA (CAP) - EMEA/H/C/002312/WS1133/0081/G; elvitegravir, cobicistat, emtricitabine, tenofovir - GENVOYA (CAP) - EMEA/H/C/004042/WS1133/0029/G; STRIBILD (CAP) - EMEA/H/C/002574/WS1133/0080/G; emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/WS1133/0011/G; emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS1133/0136/G; tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/WS1133/0174/G

Applicants: Bristol-Myers Squibb and Gilead Sciences Ltd. (Atripla), Gilead Sciences International Ltd (Eviplera, Genvoya, Odefsey, Stribild, Truvada, Viread, Descovy)

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations including: 1) update of sections 4.4 and 4.5 of the SmPC of tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Eviplera, Stribild) following the results from study GS-US-342-1167 (phase 1 study to evaluate the potential drug-drug interaction between sofosbuvir/velpatasvir (SOF/VEL) tablets and human immunodefficiency virus antiretrovirals (HIV ARVs): efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF; Atripla), emtricitabine/riplivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera), dolutegravir (DTG; Tivicay) or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF) in healthy subjects) and study GS-US-342-1326 (phase 1 study to evaluate the pharmacokinetic (PK) drug-drug interaction between SOF/VEL and HIV ARVs: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF), ritonavir-boosted darunavir (DRV/r) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), ritonavir-boosted atazanavir (ATV/r) plus FTC/TDF, ritonavir/boosted lopinavir (LPV/r) plus FTC/TDF or raltegravir plus FTC/TDF in healthy subjects); 2) update of section 4.5 for the tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey) following the results from study GS-US-342-1167. The Package Leaflets and RMPs are updated accordingly

15.3.9. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/WS1134/0137; Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/WS1134/0175

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: Worksharing variation to update section 4.5 of the SmPC for Viread and Truvada with data on interaction between emtricitabine (FTC), tenofovir disoproxil fumarate (TDF),

[40] Cytochrome P450 2B6

ledipasvir, sofosbuvir and dolutegavir based on new clinical pharmacology data from study GS-US-377-1501. This is a Phase 1, open-label, multiple-dose study that evaluated the pharmacokinetic drug-drug interaction potential between Harvoni (ledipasvir [LDV]/sofosbuvir [SOF]) and FTC/TDF+dolutegravir (DTG). The RMP version 22 for Viread and version 14 for Truvada have also been submitted

15.3.10. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS0992/0022/G; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS0992/0017/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped worksharing variation to update sections 4.4, 4.8 and 5.1 of the SmPC in order to include data from study HZC113782 (SUMMIT): clinical outcomes study comparing the effect of fluticasone furoate/vilanterol inhalation powder 100/25mcg with placebo on survival in subjects with moderate chronic obstructive pulmonary disease (COPD) and a history of or at increased risk for cardiovascular disease. In addition, section 4.8 of the SmPC is updated to add 'paradoxical bronchospasm' to the list of adverse reactions as well as section 5.1 of the SmPC to correct an error identified in the pharmacodynamic section. The Package Leaflet, Labelling and RMP (version 8.1) are updated accordingly

15.3.11. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1101/0029; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1101/0025

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 5.1 of the SmPC in order to update the safety information with the results of HZC115151 study: a 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate/vilanterol inhalation powder delivered once daily via a novel dry powder inhaler (NDPI) compared with the existing chronic obstructive pulmonary disease (COPD) maintenance therapy alone in subjects with COPD (Annex II condition) of the Relvar Ellipta and Revinty Ellipta (92/22mcg strength only). The RMP (version 8.3) is updated accordingly

15.3.12. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/II/0084

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Submission of the summary analysis report on the incidence of neoplasms with the combination of liraglutide and insulin detemir from the cardiovascular outcome trial for Victoza (liraglutide): study EX2211-3748 (LEADER: liraglutide effect and action in diabetes): a long-term, multicentre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events. The RMP (version 18) is updated accordingly to delete the important potential risk of malignant neoplasms following combination treatment with insulin detemir + liraglutide + metformin

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

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Qun-Ying Yue

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

15.3.14. Pasireotide - SIGNIFOR (CAP) - EMEA/H/C/002052/X/0030/G, Orphan

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Line extension to introduce two new strengths for the 'powder and solvent for suspension for injection pharmaceutical form' (10 mg and 30 mg) grouped with a type II variation to extend the indication to include the 'treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed' to the intramuscular injection formulations. The RMP (version 5.0) is updated accordingly

15.3.15. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0018/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Grouped variation to update section 5.1 of the SmPC to reflect the data from the post-authorisation efficacy studies (PAES) in melanoma study P001 (phase I study of pembrolizumab alone in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma), study P002 (randomized, phase II study of pembrolizumab versus chemotherapy in patients with advanced melanoma) and study P006 (a multicentre, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab in patients with advanced melanoma). Annex II and the RMP (version 6.0) are updated accordingly

15.3.16. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0025

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC to add a warning on the risk of severe skin reactions and to communicate that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported in patients treated with pembrolizumab. The Package Leaflet and the RMP (version 8.0) are updated accordingly. The submission includes a proposed DHPC and communication plan

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

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.4, 4.6, 5.1 and 5.2 of the SmPC in order to include information: use of rilpivirine in combination with a background regimen for the treatment of HIV-1 infection during pregnancy and postpartum, without dose adjustment following final results from study TMC114HIV3015 listed as a category 3 study in the RMP. This is a single arm, open-label trial to assess the pharmacokinetics of darunavir/ritonavir, etravirine, and rilpivirine in HIV-1-infected pregnant women. The Package Leaflet is updated accordingly. The RMP version 7.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce the latest renewal date in section 9 of the SmPC and the physical address of the Netherlands Local Representative in the PIL section 6.

15.3.18. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/II/0017/G

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variation including: 1) update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from previously untreated patients (PUP) based on the interim report of interventional study GENA-05 (an immunogenicity, efficacy and safety of treatment with human cell line-derived recombinant factor VIII (human-cl-rhFVIII) in previously untreated patients with severe haemophilia A). The Package Leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the Product Information throughout to bring it in line with the core Summary of Product Characteristics for human plasma-derived and recombinant coagulation factor VIII products (EMA/CHMP/BPWP/1619/1999 rev. 2) and with the latest QRD template (version 10). Moreover, the MAH proposed to combine the SmPC for all strengths and to update Annex A with detailed information on the packaging

15.3.19. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1141/0056; RISTABEN (CAP) - EMEA/H/C/001234/WS1141/0048; TESAVEL (CAP) - EMEA/H/C/000910/WS1141/0056; XELEVIA (CAP) - EMEA/H/C/000762/WS1141/0060

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC in order to add ‘bullous pemphigoid’ as a warning following the PRAC outcome for EMEA/H/C/PSUSA/2711/201408 procedure. The Labelling and the RMP (version 7) are updated accordingly

15.3.20. Sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1130/0081/G; JANUMET (CAP) - EMEA/H/C/000861/WS1130/0081/G; RISTFOR (CAP) - EMEA/H/C/001235/WS1130/0068/G; VELMETIA (CAP) - EMEA/H/C/000862/WS1130/0084/G

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variation including: 1) update of section 4.4 of the SmPC in order to add 'bullous pemphigoid' as a warning following the PRAC outcome for EMEA/H/C/PSUSA/2711/201408 procedure. The Labelling and the RMP (version 7) are updated accordingly; 2) The RMP (version 7) is updated to add a targeted questionnaire related to lactic acidosis as part of the outcome of referral procedure EMEA/H/A-31/1432 on metformin-containing medicines completed in 2016

15.3.21. Sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/II/0039

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to add 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 RMP (version 2) are updated accordingly

15.3.22. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/X/0029, Orphan

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Line extension to add a new strength of 1.25 mg (paediatric formulation). The RMP (version 7.4) is updated accordingly

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

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

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

15.3.24. Varenicline - CHAMPIX (CAP) - EMEA/H/C/000699/II/0064

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.5 and 5.1 of the SmPC in order to update the safety information based on the final results from study A3051078: a varenicline pregnancy cohort study (a prospective population-based cohort study to examine whether varenicline use

during pregnancy is associated with an increased risk of major congenital malformations in infants above that associated with smoking during pregnancy). The Package Leaflet and the RMP (version 10.1) are updated accordingly. In addition, the MAH took the opportunity to bring the Product Information in line with the latest QRD template (version 10)

15.3.25. Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0032

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.3 of the SmPC in order to reflect non-clinical carcinogenicity studies (MEA 003): 1) study 13-0322: a 26-week oral gavage carcinogenicity study with vismodegib in hemizygous CByB6F1-Tg(HRAS)2Jic mice; 2) study 13-0323: a 104-week and 52-week with a 12-week recovery phase oral gavage carcinogenicity study with vismodegib in Sprague Dawley rats. The RMP (version 12.0) is updated accordingly. Furthermore, additional routine changes (including some resulting from the assessment of RMP version 11) have been introduced

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. Afatinib - GIOTRIF (CAP) - PSUSA/00010054/201609

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.2. Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201609

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201609

Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.4. Alirocumab - PRALUENT (CAP) - PSUSA/00010423/201609

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.5. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201609

Applicant: Celgene Europe Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.6. Bivalirudin - ANGIOX (CAP) - PSUSA/00000421/201609

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.7. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201609

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.8. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201609

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.9. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201609

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Cholic acid[41] - KOLBAM (CAP) - PSUSA/00010182/201609

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.11. Cholic acid[42] - ORPHACOL (CAP) - PSUSA/00010208/201609

Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.12. Ciclosporin[43] - IKERVIS (CAP) - PSUSA/00010362/201609

Applicant: Santen Oy

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.13. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201609

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.14. Dexamethasone[44] - NEOFORDEX (CAP) - PSUSA/00010480/201609

Applicant: Laboratoires CTRS

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.15. Etravirine - INTELENCE (CAP) - PSUSA/00001335/201609

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUSA procedure

[41] Treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7α-hydroxylase (CYP7A1) deficiency indications only

[42] Treatment of inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase indications only

[43] For topical use only

[44] Treatment of symptomatic multiple myeloma indication for centrally authorised product(s) only

16.1.16. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201609

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.17. Glycopyrronium bromide[45] - ENUREV BREEZHALER (CAP); SEEBRI BREEZHALER (CAP); TOVANOR BREEZHALER (CAP) - PSUSA/00010047/201609 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.18. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201609

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.19. Indacaterol, glycopyrronium bromide - ULTIBRO BREEZHALER (CAP); ULUNAR BREEZHALER (CAP); XOTERNA BREEZHALER (CAP) - PSUSA/00010105/201609 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

16.1.20. Insulin human[46] - INSUMAN (CAP) - PSUSA/00010107/201609

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogne

Scope: Evaluation of a PSUSA procedure

16.1.21. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201609

Applicant: Basilea Medical Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

[45] Treatment of chronic obstructive pulmonary disease indication only
[46] Intraperitoneal route of administration

16.1.22. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201609

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.23. Leflunomide - ARAVA (CAP); LEFLUNOMIDE MEDAC (CAP); LEFLUNOMIDE WINTHROP (CAP) - PSUSA/00001837/201609

Applicant: Sanofi-aventis Deutschland GmbH (Arava, Leflunomide Winthrop), Medac Gesellschaft fur klinische Spezialpraparate GmbH (Leflunomide medac)

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.24. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201609

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.25. Midazolam[47] - BUCCOLAM (CAP) - PSUSA/00010118/201609

Applicant: Shire Services BVBA

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.1.26. Moroctocog alfa - REFACTO AF (CAP) - PSUSA/00002089/201608

Applicant: Pfizer Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.27. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201609

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

[47] Oromucosal solution, treatment of prolonged, acute, convulsive seizures indication(s) only

16.1.28. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201609

Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.29. Pyronaridine, artesunate - PYRAMAX (Art 58[48]) - EMEA/H/W/002319/PSUV/0014

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Caroline Laborde

Scope: Evaluation of a PSUR procedure

16.1.30. Raltegravir - ISENTRESS (CAP), raltegravir, lamivudine - DUTREBIS (CAP) - PSUSA/00010373/201609

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Retigabine - TROBALT (CAP) - PSUSA/00002624/201609

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.32. Riociguat - ADEMPAS (CAP) - PSUSA/00010174/201609

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.33. Ritonavir - NORVIR (CAP) - PSUSA/00002651/201608

Applicant: AbbVie Ltd.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.1.34. Telavancin - VIBATIV (CAP) - PSUSA/00002879/201609

Applicant: Theravance Biopharma Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.35. Tobramycin[49] - VANTOBRA (CAP) - PSUSA/00010370/201609

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.36. Trastuzumab - HERCEPTIN (CAP) - PSUSA/00003010/201609 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.37. Vinflunine - JAVLOR (CAP) - PSUSA/00003123/201609

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

None

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

16.3.1. Ajmaline (NAP) - PSUSA/00000072/201608

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

[49] Nebuliser solution, centrally authorised product(s) only

16.3.2. Budesonide, formoterol (NAP) - PSUSA/00000450/201608

Applicant(s): various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.3.3. Buserelin (NAP) - PSUSA/00000462/201608

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.4. Cilostazol (NAP) - PSUSA/00010209/201608

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. Ethinylestradiol, gestodene[50] (NAP) - PSUSA/00010145/201608

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.6. Fluocinolone acetonide[51] (NAP) - PSUSA/00010224/201608

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.7. Fosfomycin[52] (NAP) - PSUSA/00010336/201607

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

[50] Transdermal application
[51] Intravitreal implant in applicator
[52] Intravenous (IV) formulation

16.3.8. Fosfomycin[53] (NAP) - PSUSA/00010326/201607

Applicant(s): various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.9. Human plasma protease C1 inhibitor[54] (NAP) - PSUSA/00010163/201608

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.10. Lisdexamfetamine (NAP) - PSUSA/00010289/201608

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Paricalcitol (NAP) - PSUSA/00002316/201608

Applicant(s): various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.12. Timolol[55] (NAP) - PSUSA/00010439/201607

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Betaine anhydrous - CYSTADANE (CAP) - EMEA/H/C/000678/LEG 023

Applicant: Orphan Europe S.A.R.L.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of MAH's response to PSUSA/00000390/201602 (analysis of the data on patients with remethylation disorders with baseline and follow-up measures with methionine and homocysteine plasma level, issued from the Cystadane Surveillance Programme (CSP))

[53] Oral formulation
[54] Nationally authorised products
[55] Ocular preparations

16.4.2. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/LEG 039.1

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of MAH's response to LEG 039 (cumulative review on cases of liver-related events (hepatotoxicity) as requested in the recommendation of PSUSA/00002653/201509 adopted by PRAC in April 2016) as per request for supplementary information (RSI) adopted in November 2016

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)[56]

17.1.1. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSP/S/0049.2

Applicant: Horizon Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Updated PASS protocol for an open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, using data collected through European cystic fibrosis registries as per the request for supplementary information (RSI) adopted at PRAC in December 2016

17.1.2. Ethinylestradiol (NAP); levonorgestrel, ethinylestradiol (NAP) - EMEA/H/N/PSP/J/0054

Applicant(s): Teva Pharma B.V. (Seasonique), various

PRAC Rapporteur: Claire Ferard

Scope: PASS protocol for a drug utilisation study of Seasonique in Europe with the aim to assess both safety outcomes and drug utilisation patterns

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[57]

17.2.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 019.1: revised protocol for a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (study OBS14697), as per the request for supplementary information (RSI) adopted in December 2016

17.2.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin containing products compared to patients with T2DM exposed to non-SGLT2 inhibitor anti-hyperglycaemic agents

17.2.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: PASS protocol of an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin containing products compared to patients with T2DM exposed to non-SGLT2 inhibitor anti-hyperglycaemic agents

17.2.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/MEA 067.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: MAH's response to MEA 067: revised PASS protocol and questionnaire for a cross sectional physician survey (study N6987) to assess the impact of educational materials on prescribers' awareness of doses and biological monitoring recommendations and also to assess the awareness and appropriate use of both formulations (orodispersible tablets and film-coated tablets) as requested as part of X/43 (RMP, category 3 study), as per the request for supplementary information (RSI) adopted in December 2016

[57] 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. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/MEA 001.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 001.1 on a revised PASS protocol for a survey to assess physicians'/oncologists' understanding of the key conditions for the safe use of necitumumab, as per the request for supplementary information (RSI) adopted in November 2016

17.2.6. Necitumumab - PORTRAZZA (CAP) - EMEA/H/C/003886/MEA 002.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002.1 on a revised PASS protocol for an observational prospective study to assess the incidence, severity, and sequelae of all serious life-threatening identified and potential risks for necitumumab treatment in the approved indication, as per the request for supplementary information (RSI) adopted by PRAC and CHMP in November 2016

17.2.7. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 004

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PASS protocol for study C38072-AS-50026, a non-interventional phase IV study: effect of reslizumab exposure on pregnancy outcomes: active pregnancy surveillance

17.2.8. Sodium oxybate - XYREM (CAP) - EMEA/H/C/000593/MEA 019

Applicant: UCB Pharma Ltd.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Protocol for study NA0001 (EU PAS register EUPAS15024): a non-interventional PASS on the effectiveness of the educational materials

17.2.9. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/MEA/045.3

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of MAH proposal to include additional data-sets along with the British Society of Rheumatology Biologics Register (BSRBR) data to complete the post-authorisation measure. This non-interventional post-authorisation safety study aims to collect further safety data, including data about hypersensitivity, in patients who switch route of tocilizumab administration from intravenous to subcutaneous pharmaceutical forms

17.3. Results of PASS imposed in the marketing authorisation(s)[58]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[59]

17.4.1. Collagenase Clostridium histolyticum - XIAPEX (CAP) - EMEA/H/C/002048/II/0089

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report for study B1531005, a non-interventional study to evaluate the outcomes (clinical treatment success measured by goniometry assessment, recurrence rate measured by goniometry assessment, subject and physician global assessment of treatment satisfaction, complications resulting from the procedure based on the adverse event/serious adverse event (AE/SAE)) of 3 various treatment options for Dupuytren's contracture, listed as a category 3 study in the RMP. The RMP (version 13.0) is updated accordingly

17.4.2. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0009

Applicant: Samsung Bioepis UK Limited (SBUK)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final clinical study report (CSR) of study SB2-G31-RA: a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of Flixabi compared to Remicade in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy. The RMP (version 4) is updated to reflect the results from the 78 weeks CSR, to exclude 2 of the 5 registries of the pharmacovigilance plan and update the due date for the prospective observational cohort study of Flixabi in ankylosing spondylitis (AS) and Crohn's disease (CD) patients

17.4.3. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/WS0943/0009; VICTOZA (CAP) - EMEA/H/C/001026/WS0943/0041

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final results from a RMP category 3 study NNN2211-3784: liraglutide safety and surveillance programme using the Optum research database study and its sub-study on breast cancer. The RMP (version 26) is updated accordingly

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

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

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

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

17.4.5. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/II/0102

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report for study STRATIFY-2 (101JC402), an observational, longitudinal cohort study designed to gather post-marketing data on the incidence of progressive multifocal leukoencephalopathy (PML) in natalizumab-treated subjects with MS. The RMP (version 23) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[60]

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 056.2

Applicant: Genzyme Europe BV

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to MEA 056.1: interim report from a healthcare pofessional survey that measure the effectiveness of the approved safety information packet (SIP) as per the request for supplementary information (RSI) adopted in December 2016

17.5.2. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.2

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a yearly report for study BEL115467/HGS1006-C1113: a randomized, double-blind placebo-controlled large safety study, based on a protocol agreed with CHMP, evaluating over a minimum of 1 year the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus

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

17.5.3. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.6

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Third progress report covering the period from November 2015 until October 2016 for PASS NN304-4016 (EVOLVE study): an international non-interventional prospective cohort registry to evaluate the safety of treatment with Levemir (insulin detemir) in pregnant women with diabetes mellitus

17.5.4. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 265.7

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Caroline Laborde

Scope: MAH's response to MEA 265.6: interim results for study GS-EU-174-1403, a pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate and describe the management of tenofovir-associated renal and bone toxicity in chronic hepatitis B-infected adolescents aged 12 to <18 years in Europe as per the request for supplementary information (RSI) adopted in October 2016

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.11

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Valerie Strassmann

Scope: Sixth independent data monitoring committee (IDMC) status report for DIA 3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM) studies

17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.11

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Sixth independent data monitoring committee (IDMC) status report for DIA 3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)) and DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM) studies

17.6.3. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 005.3

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005.3: evaluation of a statistical analysis plan for study DSE-EDO-01-14-EU: a drug utilisation study (DUS) for exploring edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study, as per the request for supplementary information (RSI) adopted in September 2016

17.6.4. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 006.3

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 006.3: evaluation of a statistical analysis plan for study DSE-EDO-04-14-EU ETNA-AF: a non-interventional study on edoxaban treatment in routine clinical practice for patients with non valvular atrial fibrillation, as per the request for supplementary information (RSI) adopted in September 2016

17.6.5. Edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/MEA 007.3

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 007.3: evaluation of a statistical analysis plan for study DSE-EDO-05-14-EU ETNA-AF: a non-interventional study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe, as per the request for supplementary information (RSI) adopted in September 2016

17.6.6. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.4

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: MAH's responses on the statistical analysis plan (SAP) to MEA 093.3: revised PASS registry protocol for a long-term surveillance study of rituximab (Mabthera)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS) as per request for supplementary information adopted in November 2016

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

None

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

None

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0011 (without RMP)

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0020 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

18.1.3. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0020 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.1.4. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0005 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: Annual reassessment of the marketing authorisation

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[61]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Conditional renewal of the marketing authorisation

18.2.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0032 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Anidulafungin - ECALTA (CAP) - EMEA/H/C/000788/R/0033 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

18.3.2. Capecitabine - CAPECITABINE MEDAC (CAP) - EMEA/H/C/002568/R/0017 (without RMP)

Applicant: Medac Gesellschaft fuer klinische Spezialpraeparate GmbH

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/R/0042 (without RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

[61] Advanced therapy medicinal product

18.3.4. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/R/0037 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: 5-year renewal of the marketing authorisation

18.3.5. Orlistat - ALLI (CAP) - EMEA/H/C/000854/R/0054 (with RMP)

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.6. Teglutide - REVESTIVE (CAP) - EMEA/H/C/002345/R/0038 (with RMP)

Applicant: Shire Pharmaceuticals Ireland Ltd

PRAC Rapporteur: Torbjorn Callreus

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 3-6 April 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
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Jana Mladá	Member	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
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
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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
Marcel Bruch	Member	Luxembourg	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
Adam Przybylkowski	Member	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
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	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)	Member	Independent	No	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
De Bruin		scientific expert	restrictions applicable to this meeting	
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
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Veerle Verlinden	Expert - via telephone*	Belgium	No interests declared	Full involvement
Lotfi Boudali	Expert - via telephone*	France	No interests declared	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Jean-Louis Montastruc	Expert - via telephone*	France	No interests declared	Full involvement
Eva Alešík	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Anke Blumberg	Expert - in person*	Germany	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Inge Zomerdijk	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Eva Cantarero	Expert - in	Spain	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		declared	
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Karl-Mikael Kälkner	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No interests declared	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Vicky Okeefe	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. 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/