8 July 2016
EMA/PRAC/460046/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 6-9 June 2016

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 scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

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

Note on access to documents

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

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1. Introduction

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

The Chairperson opened the 6-9 June 2016 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). No new or additional conflicts were declared.

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

The PRAC Chairperson welcomed Claire Ferard and Eva Segovia as new PRAC alternates for France and Spain respectively.

1.2. Agenda of the meeting of 06-09 June 2016

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 10-13 May 2016

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 10-13 May 2016 were published on the EMA website on 1 July 2016 (EMA/PRAC/457201/2016).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. 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: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

Scope: 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

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for gadolinium-containing medicines (GdCAs) (gadobenic acid; gadobutrol; gadodiamide; gadopentetic acid; gadoteric acid; gadoteridol; gadoxetic acid; gadoversetamide (Optimark)) to review the issue of accumulation of gadolinium in the brain, its clinical consequences and the overall safety profile of GdCAs. For further background, see PRAC minutes January 2016 and PRAC minutes March 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary conclusion reached by the Rapporteurs and adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable (EMA/PRAC/195601/2016 rev.1). In addition, the PRAC adopted a list of questions (LoQ) for the ad-hoc expert group meeting scheduled on 5 September 2016.

3.2.2. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Ulla Wändel Liminga

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

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Zydelig (idelalisib) to review findings from the interim results of three clinical trials[1] together with all available safety data related to idelalisib, following an increased rate of death and serious adverse events (SAE) amongst subjects receiving idelalisib compared to control groups, observed in these clinical trials and to assess the potential impact on the benefit-risk balance of Zydelig in the approved indications and the ongoing procedure extension of indication in chronic lymphocytic leukaemia (CLL) for use in combination with ofatumumab (variation II/011). For further background, see PRAC minutes March 2016 and PRAC minutes May 2016.

Summary of recommendation(s)/conclusions

The PRAC discussed the conclusions reached by the Scientific Advisory Group on Oncology (SAG-O) held on 12 May 2016. In addition, the PRAC discussed the conclusion reached by the Rapporteurs and adopted a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable (EMA/PRAC/196144/2016 Rev. 1).

3.3. Procedures for finalisation

None

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

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Dasabuvir - EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of depression and suicidal ideation
EPITT 18670 – New signal
Lead Member State: ES

Background

[1] GS-US-312-0123: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukaemia
GS-US-313-0124: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent non-Hodgkin lymphomas
GS-US-313-0125: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS 1101) in combination with bendamustine and rituximab for previously treated indolent non-Hodgkin lymphomas

[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.

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) ribonucleic acid (RNA)-dependent RNA polymerase, indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Ombitasvir and paritaprevir are inhibitors of the hepatitis C virus (HCV). Ritonavir, which is not active against HCV, is a CYP3A[3] inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir. The combination ombitasvir, paritaprevir, ritonavir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

The post-marketing exposure for Exviera, a centrally authorised medicine containing dasabuvir, is estimated to have been more than 158,715 patient treatment courses worldwide, in the period from first authorisation in January 2015 until December 2015.

The post-marketing exposure for Viekirax, a centrally authorised medicine containing ombitasvir, paritaprevir and ritonavir, is estimated to have been more than 158,715 patient treatment courses worldwide, in the period from first authorisation in January 2015 until December 2015.

During routine signal detection activities, a signal of depression and suicidal ideation was identified by Spain, based on 2 supportive cases retrieved from the Spanish spontaneous reporting database (FEDRA). Spain confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in FEDRA, VigiLyze[4] and EudraVigilance. Taking into account that the risk of depression and suicidal ideation may be serious, that the time to onset is compatible with a causal relationship and that a positive dechallenge was observed in both supportive cases, the PRAC considered that the MAH for Exviera and Viekirax should provide a cumulative review of reported cases of depression.

Summary of recommendation(s)

- The MAH for Exviera (dasabuvir) and Viekirax, (ombitasvir, paritaprevir, ritonavir) should submit to the EMA, in the next PSUR (DLP: 14/07/2016) (PSUSA/00010363/201607 and PSUSA/00010367/201607 respectively) a cumulative review of cases reported with the standardised MedDRA[5] queries (SMQ) 'depression and suicide/self-injury'.

4.2. New signals detected from other sources

4.2.1. Dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)

Applicant: AbbVie Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of risk of drug interaction with fluindione leading to a reduced international normalized ratio (INR)
EPITT 18654 – New signal
Lead Member State: ES

[3] Cytochrome P450, family 3, subfamily A
[4] Search and analyse in VigiBase (WHO global database of individual case safety reports (ICSRs))
[5] Medical Dictionary for Regulatory Activities

Background

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) ribonucleic acid (RNA)-dependent RNA polymerase, indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Ombitasvir and paritaprevir are inhibitors of the hepatitis C virus (HCV). Ritonavir, which is not active against HCV, is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir. The combination ombitasvir, paritaprevir, ritonavir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

The post-marketing exposure for Exviera, a centrally authorised medicine containing dasabuvir, is estimated to have been more than 158,715 patient treatment courses worldwide, in the period from first authorisation in January 2015 until December 2015.

The post-marketing exposure for Viekirax, a centrally authorised medicine containing ombitasvir, paritaprevir and ritonavir, is estimated to have been more than 158,715 patient treatment courses worldwide, in the period from first authorisation in January 2015 until December 2015.

A signal of risk of drug interaction with fluindione leading to a reduced international normalized ratio (INR) was identified by EMA, based on 4 case reports of reduced INR reported in the context of co-administration of Viekirax (ombitasvir, paritaprevir and ritonavir) with fluindione. The MAH provided EMA with a summary of their preliminary investigation of the cases. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from case reports in EudraVigilance. Taking into account the biological plausibility for reduced INR values in patients treated with vitamin K antagonists due to changes in liver function, and that there was a positive dechallenge in one case, the PRAC considered that the product information of direct-acting antivirals indicated for the treatment of hepatitis C should be updated to include the need for close monitoring of INR values in patients treated with vitamin K antagonists and the MAHs should comment on a proposed wording to update their product information.

Summary of recommendation(s)

- The MAHs for Daklinza (daclatasvir), Exviera (dasabuvir), Harvoni (sofosbuvir/ledipasvir), Incivo (telaprevir), Olysio (simeprevir), Sovaldi (sofosbuvir), Victrelis (boceprevir) and Viekirax (ombitasvir/paritaprevir/ritonavir) should provide comment to the EMA, within 30 days, on the need to update the 'interaction with other medicinal products and other forms of interaction' section of the SmPC with the need for close monitoring of IRN values in patients treated with vitamin K antagonists. In addition, when applicable, the MAH should propose adjustments to other relevant information regarding vitamin K antagonists.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.
- In addition, the MAHs for Dakinza (daclatasvir), Exviera (dasabuvir), Harvoni (sofosbuvir/ledipasvir), Incivo (telaprevir), Olysio (simeprevir), Sovaldi (sofosbuvir),

Victrelis (boceprevir) and Viekirax (ombitasvir/paritaprevir/ritonavir) should continue to review the possible interactions with vitamin K antagonists in future PSURs and discuss whether further changes to the product information are warranted.

4.2.2. Riociguat - ADEMPAS (CAP)

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Signal of increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial
EPITT 18681 – New signal
Lead Member State: UK

Background

Riociguat, a stimulator of soluble guanylate cyclase (sGC), is indicated for the treatment of adult patients with WHO[6] functional class (FC) II to III with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and patients with persistent or recurrent CTEPH after surgical treatment to improve exercise capacity, and as monotherapy or in combination with endothelin receptor antagonists, for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO functional class (FC) II to III to improve exercise capacity.

The post-marketing exposure for Adempas, a centrally authorised medicine containing riociguat, is estimated to have been more than 68,621 patient-months worldwide, in the period from first authorisation in 2014 until March 2016.

A signal of increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) was identified by the UK following the termination by the MAH of study RISE-IIP on 12 May 2016. This followed a recommendation from the independent Data Monitoring Committee (DMC) for this trial, in light of data which showed increased mortality and serious adverse events among subjects receiving riociguat compared to placebo, without apparent benefits. The RISE-IIP study was a randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID[7]) in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias. The UK confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the interim results of the terminated RISE-IIP study, post-marketing data and clinical trials in the authorised indications as well as other data relating to the risk of increased mortality and SAEs in patients with PH associated with IIP, and proposals for risk minimisation measures as presented by the MAH during an oral explanation. Having considered all the available evidence, the PRAC agreed that the product information should be updated to include a contraindication for use in patients with PH associated with IIP to reflect the results of the RISE-IIP study. In addition the PRAC

[6] World Health Organization
[7] three times a day

concluded that the RMP should be udpated and that the MAH should address a list of questions.

The PRAC recommended that the MAH for Adempas should distribute a direct healthcare professional communication (DHPC) letter to inform about the results of the RISE-IIP study and to discourage off-label use in patients with PH associated with IIP.

Summary of recommendation(s)

- The MAH for Adempas (riociguat) should submit to EMA, within 30 days, a variation to include a contraindication for use in patients with PH associated with IIP as well as updates to the SmPC to reflect the results of the RISE-IIP study.
- The MAH should also distribute a DHPC according to the text and communication plan agreed with the PRAC and CHMP.
- Finally the MAH should submit to the EMA, within 90 days, a revised RMP including 'off-label use in patients with IIP, with or without PH' as an important identified risk along with proposals for pharmacovigilance acitivities to monitor off-label use. This should include consideration of whether updates are needed to the ongoing EXPERT study[8] to ensure more complete capture of data related to the indication for use. The MAH should also provide the the Independent Expert report for the RISE-IIP trial in addition to the responses to a list of questions (based on the unblinded and clean dataset).

4.3. Signals follow-up and prioritisation

4.3.1. Cisplatin (NAP)

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of peripheral arterial thromboembolic events (ATEs) and arterial occlusion
EPITT 18560 – Follow-up to January 2016

Background

For background information, see PRAC minutes of January 2016. The MAHs replied to the request for information on the signal of peripheral arterial thromboembolic events (ATEs) and arterial occlusion and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the MAHs' responses. Taking into account the limited available evidence of a drug related increase in risk from the cumulative reviews provided, the PRAC concluded that no changes to the product information of cisplatin-containing medicinal products are warranted at this time. Nevertheless, peripheral arterial disease should be considered as a potential risk associated with cisplatin therapy and MAHs of cisplatin-containing medicinal products should actively monitor these events and report them as part of the next PSUR.

Summary of recommendation(s)

- The MAHs of cisplatin-containing medicinal products should consider peripheral arterial disease as a potential risk associate with cisplatin therapy. In addition they

[8] EXPERT: EXPosurE Registry RiociguaT in patients with pulmonary hypertension. NCT02092818

should in the next PSUR (DLP: 18/12/2017) actively monitor these events and provide a summary of new cases from previous reviews, with emphasis on the cases supported by temporal association and positive re-challenge, as well as an evaluation of new studies from the literature.

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. Empagliflozin, linagliptin - EMEA/H/C/003833

Scope: Treatment of type 2 diabetes mellitus

5.1.2. Etelcalcetide - EMEA/H/C/003995

Scope: Treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy

5.1.3. Olaratumab - EMEA/H/C/004216, Orphan

Applicant: Eli Lilly Nederland B.V.

Scope (accelerated assessment): Treatment of soft tissue sarcoma

5.1.4. Palbociclib - EMEA/H/C/003853

Scope: Treatment of breast cancer

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

5.3.1. Canakinumab – ILARIS (CAP) - EMEA/H/C/001109/II/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to amend the systemic juvenile idiopathic arthritis (SJIA) indication to include treatment of active Still's disease including adult-onset Still's disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring

the annexes in line with the latest QRD template. An updated RMP (version 10) was provided as part of the application

Background

Canakinumab is a fully human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody indicated for the treatment of cryopyrin-associated periodic syndromes, systemic juvenile idiopathic arthritis (SJIA) and gouty arthritis under certain conditions.

The CHMP is evaluating an extension of the therapeutic indication for Ilaris, a centrally authorised product containing canakinumab, to include the treatment of active Still's disease including adult-onset Still's disease (AOSD) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see PRAC minutes March 2016.

Summary of advice

- The RMP version 10.1 for Ilaris (canakinumab) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses to the request for supplementary information (RSI) are submitted by the MAH.
- Given the limited knowledge on pregnancy in patients being administered canakinumab, the PRAC considered that the patient alert card should be updated to reflect the need for health professionals, including nurses concerned with immunisation, to evaluate the risk of administering live vaccines to newborns previously exposed to canakinumab in-utero. In addition, the RMP should be updated to include missing information on pregnancy and lactation with regard to the administration of live vaccines, such as the Bacillus Calmette-Guérin (BCG) vaccine, in newborns exposed in-utero to canakinumab. In addition, the MAH should specify the time period since the last administration of canakinumab during which newborns should not receive vaccination with live vaccines and to explore means to collect further pregnancy data such as using previously existing canakinumab registries combined with post-marketing data.

6. Periodic safety update reports (PSURs)

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

6.1.1. Aclidinium bromide, formoterol fumarate dihydrate – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - PSUSA/00010307/201511

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Aclidinium is a long-acting muscarinic antagonist and formoterol is a long-acting β2-adrenergic agonist. The combination aclidinium bromide/formoterol fumarate dihydrate is

indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brimica Genuair and Duaklir Genuair, centrally authorised medicines containing aclidinium bromide/formoterol fumarate dihydrate, 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 Brimica Genuair and Duaklir Genuair (aclidinium bromide/formoterol fumarate dihydrate) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'anaphylactic reaction' and 'stomatitis' as new undesirable effects with an unknown and an uncommon frequency respectively. In addition, the product information should be updated to clarify that hypersensitivity has been observed with the aclidinium bromide/formoterol fumarate dihydrate combination and not only with its mono-components. Therefore the current terms of the marketing authorisation(s) should be varied[9].
- In the next PSUR, the MAH should review all cases of 'hallucination' and consider whether any further action is necessary. In addition, the MAH should provide a detailed cumulative review of cases of 'angina' reported with the aclidinium bromide/formoterol furmarate dihydrate, aclidinium mono-product and formoterol. In this context, the MAH should propose to amend the product information as necessary or provide a justification whether the final results of the ongoing cardiovascular PASS should be awaited before updating the product information.

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

6.1.2. Aflibercept – EYLEA (CAP) - PSUSA/00010020/201511

Applicant: Bayer Pharma AG

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Aflibercept, a recombinant fusion protein, is indicated[10] for the treatment of neovascular (wet) age-related macular degeneration (AMD), and visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), as well as for the treatment of visual impairment due to diabetic macular oedema (DME) and visual impairment due to myopic choroidal neovascularisation (myopic CNV).

[9] 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
[10] As a solution for injection

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Eylea, a centrally authorised medicine containing aflibercept, 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 Eylea (aflibercept) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the 'undesirable effects' section that cases of hypersensitivity reactions including rash, pruritus, urticaria and isolated cases of severe anaphylactic/anaphylactoid reactions have been reported during the post-marketing phase. Therefore the current terms of the marketing authorisation(s) should be varied[11].
- In the next PSUR, the MAH should provide a cumulative review of cases of 'hypertension' reported on the day of the injection of aflibercept including cases of 'hypertensive crisis'. In addition, given the reported significant number of cases of multiple use of single use-only pharmaceutical forms, and considering the potential ocular consequences of such a practice, the MAH should propose additional minimisation measures.

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. Eribulin – HALAVEN (CAP) - PSUSA/00001254/201511

Applicant: Eisai Europe Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Eribulin, a non-taxane microtubule dynamics inhibitor, is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Halaven, a centrally authorised medicine containing eribulin, 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 Halaven (eribulin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'Stevens-Johnson syndrome' and 'toxic epidermal necrolysis' as new undesirable effects with an unknown

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

frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].

- In the next PSUR, the MAH should provide a detailed discussion on any new case of 'QT prolongation', 'hepatobiliary disorders' and 'urinary disorders'. In addition, the MAH should closely monitor serious skin reactions.

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. Ibrutinib – IMBRUVICA (CAP) - PSUSA/00010301/201511

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) as well as for the treatment of adult patients with CLL who have received at least one prior therapy. Ibrutinib is also indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Imbruvica, a centrally authorised medicine containing ibrutinib, 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 Imbruvica (ibrutinib) 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 closely monitor and report events of 'peripheral neuropathy' including severity, confounding factors, and therapeutic management, if any. The MAH should provide a cumulative review of cases of 'gastrointestinal bleeding' and 'gastrointestinal haemorrhage'. The MAH should also provide a cumulative review of 'progressive multifocal leukoencephalopathy', including information on diagnostic certainty, causality assessment, and consequently the need to update the product information and/or the RMP. The MAH should discuss the findings of the publication by *Fabbro SK et al.*[13] and the 5 reported cases of panniculitis following exposure to ibrutinib, in light of cases from its internal database and other studies, and comment on updating the SmPC and RMP with this safety concern. Finally the MAH should

[12] 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

[13] Fabbro SK et al. 'Panniculitis in patients undergoing treatment with the bruton tyrosine kinase inhibitor ibrutinib for lymphoid leukemias'. JAMA-Oncol 2015;1(5):684-686

discuss cases of *pneumocystis jirovecii* pneumonia/infection and cytomegalovirus pneumonia/infection from clinical trials and post-marketing experience and propose updates to the product information as appropriate. The MAH should also discuss what measures were implemented during clinical trials to manage the risk of infection.

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

6.1.5. Ketoconazole – KETOCONAZOLE HRA (CAP) - PSUSA/00010316/201511

Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

Background

Ketoconazole, a steroidogenesis inhibitor, is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ketoconazole HRA, a centrally authorised medicine containing ketoconazole, 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 Ketoconazole HRA (ketoconazole) in the approved indication(s) remains unchanged.
- Nevertheless, based on the literature data presented in the PSUR, the product information should be updated to include a new contra-indication for concomitant use with the combination of ombitasvir/paritaprevir-(ritonavir) due to the increased risk of adverse reactions, and to include new interactions with ibrutinib, crizotinib and ombitasvir/paritaprevir in the 'interaction with other medicinal products and other forms of interaction' section. Therefore the current terms of the marketing authorisation(s) should be varied[14].

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. Nintedanib – VARGATEF (CAP) - PSUSA/00010318/201511

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure

Background

[14] Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Nintedanib, a protease kinase inhibitor, is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vargatef (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'gamma-glutamyltransferase liver enzyme' to the existing warning on the elevation of liver enzymes and to include 'increased gamma-glutamyltransferase' as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should monitor all adverse reactions involving co-administration of nintedanib and cyclophosphamide closely and discuss any findings in the context of study 1199.123[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. Simeprevir – OLYSIO (CAP) - PSUSA/00010255/201511

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Background

Simeprevir, a hepatitis C virus (HCV) NS3/4A serine protease inhibitor, is indicated in combination for the treatment of chronic hepatitis C (CHC) in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Olysio, a centrally authorised medicine containing simeprevir, 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 Olysio (simeprevir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include in the 'undesirable effect' section reports of hepatic decompensation and hepatic failure during Olysio

[15] Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] Phase 2 study in patients with ovarian cancer who have received multiple prior lines of therapy and who are not suitable for standard intravenous (i.v.) chemotherapy

combination therapy in the post-marketing setting. Therefore the current terms of the marketing authorisation(s) should be varied[17].

- In the next PSUR, the MAH should provide a root cause analysis of accidental overdose (patients taking simeprevir twice daily instead of once daily) and a discussion of whether any action is required. The MAH should also provide a cumulative review of cases of bradycardia as well as a causality assessment of any further cases of hepatic failure/decompensation. In addition, the MAH should provide a detailed analysis of cases of hepatic dysfunction and a discussion on whether stricter recommendations for patient monitoring is warranted. Finally, the MAH should provide a cumulative review of reports of changes in international normalised ratio (INR) with concomitant use of vitamin K antagonists, and any reports specifically reporting a drug-drug interaction with vitamin K antagonists. In this context, the MAH should propose adjustments to the product information on interactions with vitamin K antagonists as warranted.

  See also Signal 4.2.1.

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

6.1.8. Trametinib – MEKINIST (CAP) - PSUSA/00010262/201511

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Trametinib, a protein kinase inhibitor, is indicated in monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mekinist, a centrally authorised medicine containing trametinib, 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 Mekinist (trametinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cases of acute, severe left ventricular dysfunction due to myocarditis reported in patients treated with trametinib in combination with dabrafenib, and to include 'myocarditis' as a new undesirable effect with an unknown frequency for trametinib and dabrafenib combination therapy. Therefore the current terms of the marketing authorisation(s) should be varied[18].

[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] 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

- In the next PSUR, the MAH should present all cases of serious skin toxicity and serious hepatic events, regardless of whether the MAH considers there are possible alternative causes or confounding factors. The MAH should include all relevant cases, including those in patients with pre-existing cardiovascular disease, when reviewing new information on the important identified risk 'left ventricular systolic dysfunction'. Finally the MAH should provide a review of serious cases of hypersensitivity.
- The MAH should update the RMP by deleting 'hepatic failure' as an important potential risk and discuss any cases of hepatic failure and other serious drug-induced liver toxicity as part of the important identified risk 'hepatic events' within the next RMP update.

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. Vedolizumab – ENTYVIO (CAP) - PSUSA/00010186/201511

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Vedolizumab, a humanized monoclonal antibody, is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis as well as for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant of either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Entyvio, a centrally authorised medicine containing vedolizumab, 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 Entyvio (vedolizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an updated RMP to add 'liver injury' as an important potential risk and provide a detailed discussion of this safety. In addition, the MAH should include proposals for implementing a targeted follow-up questionnaire for clinical trial and post-marketing events of hepatobiliary disorders and hepatitis with autoimmune features.

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.

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

6.2.1. Sevelamer – RENAGEL (CAP), RENVELA (CAP), SEVELAMER CARBONATE ZENTIVA (CAP), TASERMITY (CAP), NAP - PSUSA/00002697/201510

Applicant: Genzyme Europe BV (Renagel, Renvela, Sevelamer Carbonate Zentiva, Tasermity), various

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

Background

Sevelamer, a non-absorbed phosphate binding crosslinked polymer free of metal and calcium, is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis as well as in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥1.78 mmol/l under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Renagel, Renvela, Sevelamer Carbonate Zentiva and Tasermity, centrally authorised medicines containing sevelamer, and nationally authorised medicines containing sevelamer, 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 sevelamer-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add a warning regarding inflammatory gastrointestinal disorders associated with the presence of sevelamer crystals. Therefore the current terms of the marketing authorisations should be varied[19].
- In the next PSUR, the MAHs should consider a baseline summary of safety concerns for important identified risks, important potential risks and missing information. The MAHs should review their summary of safety concerns in line with a proposed list of baseline safety concerns and update their RMP accordingly, as applicable.

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

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

6.3.1. Acitretin (NAP) - PSUSA/00000051/201510

Applicant: various

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

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Acitretin, a synthetic aromatic analogue of retinoic acid, is indicated for the treatment of severe forms of psoriasis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing acitretin, 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 acitretin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'dysphonia' as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAHs should provide a detailed assessment on the effectiveness of the pregnancy prevention programme (PPP). In addition, the MAH Actavis should provide further details on missing pregnancy cases and additional information available on compliance with contraceptive methods in the reported pregnancy cases. The MAH Aurobindo should comment on the observational, multicentre, cross-sectional study initiated to assess actual adherence to the conditions of prescription and supply for acitretin based on data from pharmacists and patients.

Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is required, and the EURD list should be updated accordingly. The next PSUR(s) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.3.2. Didanosine (NAP) - PSUSA/00001054/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Didanosine, a nucleoside reverse transcriptase inhibitor (NRTI), is indicated for the treatment of human immunodeficiency virus (HIV)-1 infection in combination with other antiretroviral agents under certain conditions.

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

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of didanosine-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH Bristol-Myers Squibb (BMS) should submit to the EU NCAs, within 90 days, a variation to amend the 'fertility, pregnancy and lactation' section of the product information to further strengthen the current wording and reflect the results of further investigations regarding the risks of 'birth defects' and 'cancer'. Moreover, the MAH should address the relevance of maintaining animal data in the pregnancy section of the product information.

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

6.3.3. Ivermectin (topical use) (NAP) - PSUSA/00010376/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Ivermectin, a macrocyclic lactone, is indicated in topical use for the treatment of inflammatory lesions of rosacea (papulopustular) in adult patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing ivermectin for topical use, 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 ivermectin-containing medicinal products (topical use) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'erythema' as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should detail the search criteria for literature monitoring and closely monitor reported cases of 'eye disorders', 'nervous system disorders', 'gastrointestinal disorders' and 'respiratory' with a particular focus on cases related to application close to the eyes or the nasal mucosa or the mouth resulting in accidental ingestion. In this context, the MAH should propose to update the product information as applicable and consider upgrading 'accidental oral ingestion' from an important

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

potential to an important identified risk. In addition, the MAH should provide the outcome of cases of ivermectin exposure during pregnancy.

The next PSUR(s) 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.

6.3.4. Methylphenidate (NAP) - PSUSA/00002024/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Methylphenidate, a psychostimulant centrally active sympathomimetic, is indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing methylphenidate, 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 methylphenidate-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide detailed reviews of cases of 'self-injurious behaviour', 'cardiomyopathy', 'rhabdomyolysis' as well as interactions with 'antacids and H_2 receptor blockers and proton-pump inhibitors'. In addition, the MAHs should provide a detailed review of cases of 'serotonin syndrome' and drug-induced liver injury' and propose to update the product information as applicable. The MAHs should also discuss the potential underlying causes of lack of efficacy. Finally, the MAHs of longer-acting formulations should provide detailed information on the release profile of their formulations in terms of relative gastric acidity, and should consider the potential impact on efficacy of any change of the release profile and propose to update the product information as applicable.
- Considering the seriousness of the event, the PRAC recommended to request the MAHs to submit to the NCAs, within 90 days, a cumulative review of cases of 'priapism' and associated terms with additional information on the methylphenidate-containing medicinal product formulation involved.
- The MAHs of medicinal products with an RMP in place should update their RMP in accordance with the outcome of this PSUSA procedure within an upcoming regulatory procedure affecting the RMP and no later than within 90days following the conclusions of the current PSUSA procedure.

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

6.3.5. Metoclopramide (NAP) - PSUSA/00002036/201510

Applicant: various

PRAC Lead: Ingebjørg Buajordet

Scope: Evaluation of a PSUSA procedure

Background

Metoclopramide, a dopamine-receptor (D2) antagonist, is indicated in adults for the prevention of delayed chemotherapy-induced nausea and vomiting (CINV), the prevention of radiotherapy induced nausea and vomiting (RINV), as well as for the symptomatic treatment of nausea and vomiting, including acute migraine-induced nausea and vomiting under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing metoclopramide, 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 metoclopramide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'transient increase in blood pressure' as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAHs should consider adding 'hypertension in patients with no phaeochromocytoma' as an important identified risk. The MAH Amdipharm should provide a causality assessment for 'agitation', 'anxiety', 'dyspnoea', 'muscle spasm' and 'tremor' events. The MAH Techni-Pharm should perform a review of relevant publications relating to the efficacy and safety of metoclopramide.
- Considering the seriousness of the event, the PRAC recommended to request MAHs of fixed-dose combinations containing metoclopramide to amend their product information to reflect the risk of 'transient increase in blood pressure', as other components are not expected to reduce a possible blood pressure rise induced by metoclopramide.

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

6.3.6. Perindopril (NAP) - PSUSA/00002354/201510

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

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

Background

Perindopril, a long-acting angiotensin-converting enzyme (ACE) inhibitor, is indicated for the treatment of hypertension and congestive heart failure.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing perindopril, 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 perindopril-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on concomitant use with mTOR[23] inhibitors (e.g. sirolimus, everolimus and temsirolimus), due to the increased risk of angioedema. In addition, interactions with racecadotril should be also added due to the increased risk of angioedema. Moreover, 'psoriasis aggravation' should be added as a new undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[24].
- In the next PSUR, the MAHs should discuss the frequency for 'thrombocytopenia' and 'acute kidney injury' as undesirable effects. The MAHs should also provide detailed analyses of cases of 'dysphagia', 'insomnia', 'dehydration' and 'decreased appetite'. In addition, all MAHs should present further their causality assessment methods. Finally, the MAHs should provide a detailed review of the publications from *Fralick M et al*[25] and *A.Gouraud and al.*[26] and propose to amend the product information as applicable.

Considering that data from PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended did not raise any specific safety concerns, the PRAC agreed that no further PSURs are required for those products. This will be reflected in the EURD list. The next PSUR(s) 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.

6.3.7. Rabeprazole (NAP) - PSUSA/00002601/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

[23] Mammalian target of rapamycin
[24] Update of SmPC section 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[25] Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study. Fralick M, Macdonald EM, Gomes T, Antoniou T, Hollands S, Mamdani MM, Juurlink DN; Canadian Drug Safety and Effectiveness Research Network. BMJ. 2014 Oct 30;349:g6196
[26] Association of angiotensin-converting enzyme inhibitor associated angioedema with racecadotril use. A.Gouraud and al. 2015 Fundamental and clinical pharmacology

Rabeprazole, a proton-pump inhibitor (PPI), is indicated for the treatment of gastroesophageal reflux disease (GERD), gastric and duodenal ulcer, Zollinger-Ellison syndrome, and in combination with antibiotics for the eradication of *Helicobacter pylori*.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing rabeprazole, 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 rabeprazole-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of cases of 'thromboembolic events', 'microscopic colitis', 'fundic gland polyps', 'enterocolitis haemorrhagic' as well as of 'hypertension' together with a discussion on the available evidence from the scientific literature concerning a potential mechanism of PPIs. The MAH should also provide a detailed review of unconfounded cases concerning unlisted 'blood dyscrasias' and propose to update the product information as applicable. In addition, the MAH should provide detailed analyses of cases of 'infection' together with preclinical information suggesting a mechanism for a potentially increased risk for infections as well as 'hypersensitivity, food intolerance' in the context of proton-pump inhibitors use. Moreover, the MAH should provide a detailed analysis on drug interactions. Finally, based the recent publication by *Lazarus B et al*[27], the risk of chronic renal failure should be closely monitored by analysing all cases and available literature.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I. 16.4.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[28]

7.1.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/044

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

[27] Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME. JAMA Intern Med. 2016 Feb 1;176(2):238-46. doi: 10.1001/jamainternmed.2015.7193. PMID: 26752337

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

Scope: Protocol for a prospective non-interventional post-authorisation safety study (study CC-5013-MDS-010), designed as myelodysplastic syndromes (MDS) disease registry of patients with transfusion-dependent international prognostic scoring system (IPSS) low or intermediate-1-MDS and isolated deletion (5q)

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 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.

The PRAC adopted the draft protocol for a non-interventional PASS (study CC-5013-MDS-010) designed as myelodysplastic syndromes (MDS) disease registry of patients with transfusion dependent international prognostic scoring system (IPSS) low or intermediate-1-MDS and isolated deletion (5q) in April 2014. The MAH has submitted a substantial protocol amendment to revise various timelines because of recruitment challenges, the inclusion criteria and finally the MAH has changed the time origin in the survival analysis from 'time since the first dose of treatment' to 'time since the first dose of treatment after signature of the informed consent form (ICF)'. For further background, see PRAC minutes April 2014.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 4.0 in accordance with Article 107 of Directive 2001/83/EC, objected to the draft amended protocol for the above listed medicinal product(s), as the Committee considered that the design of the study did not fulfil the study objectives. The PRAC did not consider acceptable the MAH's proposal to add recommendations on 2 FISH tests with 2 different probes to be performed taking into account that an additional FISH test does not ensure isolation of a 5q deletion and is not performed in clinical practice. The MAH should also plan analyses taking into account both the exposure time for all medications after MDS diagnosis and time from MDS diagnosis, and clarify the proposed timelines for submission of the primary analyses vis a vis the submission of the final clinical study report. The PRAC therefore recommended that:
- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 30 days-assessment timetable will be applied.

7.1.2. Susoctocog alfa – OBIZUR (CAP) - EMEA/H/C/PSP/0043

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PASS protocol for a prospective, non-interventional study to collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia treated with Obizur (study 241501).

Background

Obizur, a centrally authorised medicine containing susoctocog alfa, a recombinant, B-domain deleted porcine sequence factor VIII, is indicated in adults for the treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to factor VIII.

A protocol for a surveillance programme/registry to collect and analyse immediate and long-term data on clinical efficacy and safety of all patients with acquired haemophilia treated with Obizur was submitted by the MAH in accordance with the conditions of the marketing authorisation(s).

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the revised protocol for the above listed medicinal product(s).

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[29]

See Annex I.17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[30]

7.3.1. Cyproterone, ethinylestradiol (NAP) - EMEA/H/N/PSR/J/0003

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Results of a drug utilisation study (DUS) (database) for cyproterone/ethinylstradiol to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription

Background

In line with the conclusions of a referral under Article 107i of Directive 2001/83/EC conducted by the PRAC in 2013 for cyproterone/ethinylestradiol-containing medicines (EMEA/H/107i/1357), MAHs were required to conduct a drug utilisation study (DUS) to characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers, and to assess the main reasons for prescription. The draft protocol for this study was assessed by the PRAC, followed by the submission of the final study results for assessment by the PRAC. For background information, see PRAC minutes April 2014, PRAC minutes September 2014 , PRAC minutes October 2014, PRAC minutes December 2014, PRAC minutes April 2015 and PRAC minutes April 2016.

Based on the assessment of the final report of the non-interventional PASS, the PRAC considered that a request for supplementary information should be requested before a recommendation can be made.

Summary of advice

[29] 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
[30] In accordance with Article 107p-q of Directive 2001/83/EC

- Based on the review of the final report of the non-interventional PASS, the PRAC considered by consensus that supplementary information should be requested before a recommendation can be made.
- The PRAC considered that based only on the database DUS, no clear conclusions can be drawn regarding prescribing practices for the medicinal product during typical clinical use and the assessment of the main reason for prescription. The results should be further discussed in combination with the upcoming results from the survey DUS to prescribers. The MAH should provide the indication for prescription in the concomitant-use subgroup (patients with concomitant use of cyproterone/ethinylestradiol with other hormonal contraceptives) and comment on the apparent ongoing off-label use despite the risk minimisation measures in place.
- The MAH should submit responses to the request for supplementary information within 15 days to the EMA. A 60 days-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[31]

7.4.1. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/II/0038

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report for study CA184242: a risk minimisation tool effectiveness evaluation survey. The RMP (version 12) is updated accordingly.

Background

Yervoy is a centrally authorised medicine containing ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

The MAH had committed to perform the following non-interventional PASS: study CA18424, a patients and HCPs survey, as listed in the RMP, to assess the effectiveness of the additional risk minimisation measures agreed at the time of granting of the marketing authorisation. The Rapporteur assessed the MAH's answers to the request for supplementary information on the final results of study CA18424, a PASS to assess the effectiveness of the additional risk minimisation measures agreed at the time of granting of the marketing authorisation. For background information, see PRAC minutes February 2016.

Summary of advice

- The PRAC discussed the MAH's responses to the request for supplementary information as well as the feedback received from learned societies on the current educational materials. Health care professionals (HCP) supported the maintenance of the HCP brochure as an important tool to minimise the risk of immune-related adverse reactions. In addition HCPs and patients also supported maintaining the patient information brochure (including the alert card).

[31] 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

- The PRAC agreed on a further list of questions to the MAH. As part of the request for supplementary information, the MAH should provide an updated RMP including updated educational materials. The final version of the educational materials should be approved by the national competent authorities during national implementation of the updated educational materials in line with GVP module V on Risk Management Systems. In particular the HCP brochure should be updated.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[32]

See Annex I.17.4.

7.6. Others

7.6.1. Gadoversetamide – OPTIMARK (CAP) - EMEA/H/C/000745/ANX 014.7

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Almath Spooner

Scope: From R/012: revised protocol for study ALS-Gd64/001 as per request for supplementary information adopted in December 2015

Background

Gadoversetamide is a chelate containing gadolinium indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver.

As part of a referral procedure under Article 31 of Directive 2001/83/EC completed in 2010 (EMEA/H/A-31/1097), the CHMP agreed that further studies were warranted to assess the retention of gadolinium in bone and skin. Studies were initiated, in particular, ALS-Gd64-001[33] led by a consortium of MAHs, including the MAH for Optimark (gadoversetamide). The PRAC discussed amendments to the protocol at the December 2015 PRAC meeting and requested further protocol amendments and conditions for submission of interim analyses. For further background, see PRAC minutes May 2015, PRAC minutes July 2015, and PRAC minutes December 2015.

Summary of advice

- Based on the review of the amended protocol and additional details submitted by the consortium of MAHs, the PRAC considered the revised protocol as acceptable with the planned interim analysis.
- The MAHs should notify the EMA as soon as sufficient data are available for the interim analysis as planned in the updated protocol and at that time agree on a timeline for submission of the interim analysis data.

See also under 11.2.1. Gadolinium-containing contrast agents (GdCAs).

[32] In line with the revised variations regulation for any submission before 4 August 2013.
[33] Exploratory evaluation of the potential for long-term retention of Gadolinium in the bones of patients who have received Gadolinium based Contrast Agents according to their medical history.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders of centrally authorised products for human use

Action: For adoption of the confidential human-pharmacovigilance inspection programme 2016-2019 (first revision 2016)

Discussion/Summary of advice

The PRAC agreed the list of planned pharmacovigilance inspections 2016-1019, first revision. This list is subsequently due for agreement at CHMP.

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: PRAC consultation on a variation to update section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly.

Background

Posaconazole is a lanosterol 14α-demethylase (CYP51) inhibitor indicated for the treatment of fungal infection in adults (invasive aspergillosis, fusariosis, chromoblastomycosis and mycetoma, coccidioidomycosis as well as oropharyngeal candidiasis under certain conditions). Noxafil (posaconazole) is also indicated for the prophylaxis of invasive fungal infections in patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) as well as in hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease under certain conditions.

A type II variation proposing to update the product information of Noxafil, posaconazole, is under evaluation at the CHMP in order to strengthen the wording on non-interchangeability of the oral formulations based on new reports of medication errors related to confusion in prescribing and dispensing posaconazole tablets and oral suspension. The PRAC was requested to provide advice on this variation to the CHMP. For further background, see PRAC minutes March 2016.

Summary of advice

- Based on the review of the available information, the PRAC considered that Noxafil, posaconazole tablets and oral suspension are not interchangeable due to possible inadvertent overdosing or underdosing, with a risk of serious adverse drug reactions or lack of efficacy. In that context, the PRAC agreed on the content of a direct healthcare professional communication (DHPC) together with a communication plan to minimise the risk of medication errors arising from confusion between the two oral formulations of posaconazole.

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

None

10.3. Other requests

10.3.1. Dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/LEG 001; FORXIGA (CAP) - EMEA/H/C/002322/LEG 019 dapagliflozin, metformin – EBYMECT (CAP) - EMEA/H/C/004162/LEG 001; XIGDUO (CAP) - EMEA/H/C/002672/LEG 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: PRAC consultation on the assessment of the risk of toe amputation with dapagliflozin-containing medicinal products in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicinal products

Background

Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

Following the initiation in April 2016 of a referral procedure under Article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing products on the risk of lower limb amputation primarily of the toe, observed in a cardiovascular outcomes clinical trial, a list of questions was addressed to the MAH of dapagliflozin-containing products in order to further investigate any possible evidence of an increased risk of lower limb amputations associated with other medicinal products of the SGLT2 inhibitors class. For further background, see PRAC minutes April 2016. At the current meeting, the PRAC discussed the MAH's responses to the list of questions and their assessment.

Summary of advice

- Based on the review of the MAH's responses to the list of questions, the PRAC considered that further information was necessary before a conclusion can be drawn. Follow-up discussion is planned in July 2016.

10.3.2. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/LEG 006 empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/LEG 004

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: PRAC consultation on the assessment of the risk of toe amputation with empagliflozin-containing medicinal products in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicinal products

Background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment in adults with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

Following the initiation in April 2016 of a referral procedure under Article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing products on the risk of lower limb amputation primarily of the toe, observed in a cardiovascular outcomes clinical trial, a list of questions

was addressed to the MAH of empagliflozin-containing products in order to further investigate any possible evidence of an increased risk of lower limb amputations associated with other medicinal products of the SGLT2 inhibitors class. For further background, see PRAC minutes April 2016. At the current meeting, the PRAC discussed the MAH's responses to the list of questions and their assessment.

Summary of advice

- Based on the review of the MAH's responses to the list of questions, the PRAC considered that further information was necessary before a conclusion can be drawn. Follow-up discussion is planned in July 2016.

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

11.2.1. Gadolinium-containing contrast agents (GdCA): Gadobenate dimeglumine; gadobutrol; gadodiamide; gadopentetic acid dimeglumine, gadoteric acid (intra-articular formulation); gadoteric acid (intravenous and intravascular formulations); gadoteridol; gadoxetic acid disodium (NAP)

Applicant: various

Lead member: Rafe Suvarna

Scope: PRAC consultation on a post-authorisation measure to conduct further clinical studies to assess the retention of gadolinium in bone resulting from the 2010 referral procedures under Article 20 of Regulation (EC) 726/2004 and Article 31 of Directive 2001/83/EC for gadolinium-containing contrast agents

Background

Gadolinium containing contrast agents (GdCAs) are intravenous contrast agents for use in image enhancement of MRI and magnetic resonance angiography (MRA). An Article 31 referral for GdCAs was completed in 2010 (EMEA/H/A-31/1097), focused on measures to minimise the risk of nephrogenic systemic fibrosis (NSF) in specific patient groups, and investigation of concerns regarding accumulation of gadolinium in bone and skin tissue. Studies were initiated, ALS-Gd64-001[34] led by a consortium of MAHs, including the MAH for Optimark (gadoversetamide), and GMRA-102 concerning two products authorised by

[34]Exploratory evaluation of the potential for long-term retention of gadolinium in the bones of patients who have received gadolinium based contrast agents according to their medical history

national procedures. Due to slow rates of patient recruitment for both studies, revised protocols are being discussed. For further background, see PRAC minutes May 2015, PRAC minutes July 2015 and PRAC minutes December 2015.

Summary of advice

- Based on the review of the amended protocol and additional details submitted by the MAH, the PRAC considered the revised protocol as acceptable with the planned interim analysis. The MAHs should notify the EMA, as soon as sufficient data are available for the interim analysis as planned in the updated protocol. In addition, the MAHs should agree on a timeline for submission of the interim analysis data.

For further background, please refer to 7.6.1. Gadoversatamide – OPTIMARK (CAP).

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC working group - Recommendations on efficiency of plenary meetings – best practice guide

PRAC lead: Martin Huber, Rafe Suvarna, Ulla Wändel Liminga

Following the adoption at PRAC in May 2016 (see PRAC minutes May 2016) of the best practice guidance (BPG) on the Committee efficiency, the PRAC working group composed of EMA delegates and EMA representatives presented to PRAC an implementation plan for the BPG including goals to measure compliance with the recommendations. The PRAC agreed with the implementation plan, which includes an update on a three monthly basis on data collected on quantitative measures.

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

12.3.1. Working Party with Healthcare Professionals' Organisations (HCPWP) and Working Party with Patients' and Consumers' Organisations (PCWP) - Nomination of PRAC representative(s)

The EMA Secretariat launched a call at PRAC for nominating representative(s) to the PCWP and HCPWP for the period of 2016-2019. The PRAC endorsed the nominations of the PRAC delegates appointed by the EC representing patients' organisations: Marco Greco and Albert van der Zeijden as well as PRAC delegates appointed by the EC representing healthcare professionals: Raymond Anderson and Kirsten Myhr. One PRAC representative of the patients' organisations together a PRAC representative of the healthcare professionals will attend PCWP meetings. The same applies for HCPWP meetings.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst; Margarida Guimarães

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

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version June 2016 reflecting the PRAC 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 in June 2016, the updated EURD list was adopted by the CHMP and CMDh at their June 2016 meetings and published on the EMA website on 30/06/2016, 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. Good Pharmacovigilance Practice (GVP) module IX on Signal management – revision 1 and addendum

PRAC lead: Sabine Straus

Following the previous PRAC discussion on the draft GVP module IX on signal management (revision 1) as well as its Addendum I on 'methodological aspects of signal detection from spontaneous reports of suspected adverse reactions' (see PRAC minutes April 2016), at the organisational matters teleconference held on 23 June 2016 the draft revised documents were presented to PRAC for adoption. Further adjustments were discussed, in particular procedural options for notification of signals by MAHs. As next steps, PRAC will adopt the draft final documents by written procedure, and following adoption at the level of the European Risk Management Strategy Facilitation Group (ERMS FG) and the EMA, the documents will be finalised in order to initiate the public consultation.

Post-meeting note: the draft GVP module IX on signal management (revision 1) and GVP Module XI Addendum I on 'methodological aspects of signal detection from spontaneous reports of suspected adverse reactions' were adopted by PRAC by written procedure on 30/06/2016 and released on the EMA website for public consultation on 08/08/2016.

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

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 23 June 2016, the PRAC was updated on the outcome of the June 2016 SMART Working Group (SMART WG) work stream WS1. The SMART WG WS1 discussed the Best practice guidance on using PRAC plenary time efficiently to optimise the handling of PRAC adoption of signal recommendation outside plenary meetings (e.g. templates improvement). The SMART WG WS1 continued its discussion on designated medical events (DME) and revision of the list. With regard to SMART WG WS2-3, the group further refined the draft 'GVP Addendum I on methodological aspects of signal detection from spontaneous reports of suspected adverse reactions'. The group also worked further on the guideline on 'electronic reaction monitoring reports

(eRMR) user manual' and Guideline on 'screening for adverse drug reactions in EudraVigilance' that will come to PRAC at its September 2016 meeting.

12.12. Adverse drug reactions reporting and additional reporting

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

Post-meeting note: The updated additional monitoring list was published on 29/06/2016 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 February 2016), the EMA secretariat presented a further update on the audit plan. The PRAC was informed that the project had undergone some delays including a rescheduling of some key milestones and timelines (e.g. EV stakeholder testing, EV audit, EMA Management Board decision) due to the need to optimise the performance of the new EV system, leading to a release of the enhanced EV system in Q4 2017 (instead of Q3 2017).

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – non-interventional imposed PASS final results - new procedure under 107q of Directive 2001/83/EC - consultation on main milestones

PRAC lead: Valerie Strassmann

The PRAC was consulted on a draft proposal for a new procedure assessing non-interventional imposed PASS final study results falling under Article 107q of Directive 2001/83/EC for which the PRAC is the designated Committee to perform the evaluation and conclude on a recommendation, which can result in changes to the conditions of the marketing authorisation (MA) via a variation, suspension or revocation. The proposal was developed by the EMA Secretariat together with relevant PRAC members taking into account recent experience with the first submissions received. The PRAC discussed the key milestones that include the procedural timetable to follow, the early involvement of the CHMP or CMDh[35] to ensure a smooth link between Committees as well as a draft PRAC/Rapporteur Assessment Report (AR) template. The PRAC agreed on the start of a pilot phase to ensure the procedure is fit for purpose. PRAC members were invited to provide written comments on the draft AR template by 30 June 2016.

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public hearings - preparation of PRAC public hearings dry-run

As a follow-up to the previous PRAC discussion on the organisation of a mock-up (or dry-run) public hearing (see PRAC minutes May 2016), the EMA Secretariat provided to PRAC some final organisational details in advance of the July 2016 PRAC meeting.

12.18.2. Safety communication

None

[35] Depending of the route of marketing authorisation the medicinal products under evaluation were authorised (via the centralised procedure or via mutual recognition, decentralised or national procedure)

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Good Pharmacovigilance Practices (GVP) – revised PRAC process for GVP modules in 2016/2017 - update on GVP status overview

At the organisational matters teleconference held on 23 June 2016, the EMA secretariat presented to PRAC an overview of the GVP status following the implementation of the revised EU network governance for pharmacovigilance in April 2016 (see PRAC minutes March 2016). The PRAC was provided with an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption.

12.20.2. Good Pharmacovigilance Practices (GVP) – revised PRAC process for GVP modules in 2016/2017 - GVP Module V on Risk Management Plans and GVP module XVI on risk Communication: overlap and future scopes

At the organisational matters teleconference held on 23 June 2016, the EMA secretariat presented to the PRAC an overview of the overlap between GVP module V on 'Risk Management Systems (Rev. 1)' currently under review (public consultation ended on 31 May 2016) and GVP Module XVI on 'Risk minimisation measures: selection of tools and effectiveness regarding indicators (Rev. 1)' and the future proposed scopes of these two modules in order to avoid duplication and inconsistencies regarding routine risk minimisation measures and additional risk minimisation measures while cross references between the two GVP modules should be kept where relevant. The PRAC welcomed the proposal.

12.20.3. Good Pharmacovigilance Practice (GVP) Chapter P.II. on biologicals

PRAC lead: Sabine Straus

Following the last discussion on the draft GVP product- or population-specific considerations II on biological medicinal products (see PRAC minutes October 2015), the EMA secretariat presented to the PRAC the revised document following the public consultation that ended in February 2016 as well as comments from the Biosimilar Medicinal Products Working Party (BMWP) and the Biologics Working Party (BWP) dated May 2016. Following discussion, the PRAC agreed with the draft revised GVP product- or population-specific considerations II on biological medicinal products planned for publication and implementation in August/September 2016 following adoption at the level of the European Risk Management Strategy Facilitation Group (ERMS FG) and the EMA.

Post-meeting note: On 4 August 2016, the final Guideline on GVP 'Product- or Population-Specific Considerations II: Biological medicinal product' (EMA/168402/2014) was published on the EMA website. It came into force on 16 August 2016.

12.20.1. EMA Procedure Management department – optimising operating model

As a follow-up to the discussion in April 2016 (see PRAC minutes April 2016), EMA further updated the PRAC on the new operating model for procedure management to improve support for evaluation procedures effective since 1 June 2016 and provided the PRAC with the detailed list of procedure managers and procedure assistants allocated to each medicinal product authorised/submitted via the centralised route.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[36]

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[37].

14.1.1. Olanzapine – ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of restless leg syndrome (RLS)
EPITT 18659 – New signal
Lead Member State: FI

14.1.2. Pazopanib – VOTRIENT (CAP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Signal of polycythaemia
EPITT 18660 – New signal
Lead Member State: DK

[36] 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
[37] 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

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. Allogeneic T cells genetically modified to express suicide gene – EMEA/H/C/002801, Orphan

Applicant: MolMed SpA, ATMP[1]

Scope: Treatment in haploidentical haematopoietic stem cell transplantation

15.1.2. Docetaxel - EMEA/H/C/004086

Scope: Treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer

15.1.1. Emtricitabine, tenofovir disoproxil - EMEA/H/C/004137

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

15.1.1. Miglustat - EMEA/H/C/004016

Scope: Treatment of Gaucher disease

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

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

15.2.1. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/II/0041/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a revised RMP in order to change the scope of the pregnancy registry BEL114256 (category 3 study), to amend the due dates for studies HGS1006-C1074 and BEL116559. In addition, the MAH took the opportunity to correctly reflect the status of study BEL116027 (treatment Holiday) from planned to ongoing

15.2.2. Colistimethate sodium – COLOBREATHE (CAP) - EMEA/H/C/001225/II/0021

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

[1] Advanced-therapy medicinal product

Scope: Update of the RMP (version.6.0) in order to add information on the first interim report for study CLB-MD-05 (an open-label observational safety study of Colobreathe compared with other inhaled antipseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries, MEA 009) and the protocol for study CLB-MD-08 (a post-authorisation registry based safety study to evaluate the effectiveness of the risk minimisation educational materials, including DVD and patient and healthcare professional guide, implemented in the EU for Colobreathe)

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. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/II/0020

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerisation based on the phase III clinical study ALA-AK-CT007. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet

15.3.2. Arsenic trioxide – TRISENOX (CAP) - EMEA/H/C/000388/II/0058

Applicant: Teva B.V.

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the induction of remission, and the consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox. As a consequence, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated regarding the posology, efficacy and safety information and warnings. In addition, a Risk Management Plan is introduced. The Package Leaflet is updated accordingly

15.3.3. Atazanavir, cobicistat – EVOTAZ (CAP) - EMEA/H/C/003904/II/0007/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final study reports for two category 3 studies: study GS-US-216-114 (a phase III randomised, double-blind study to evaluate the safety and efficacy of GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir each administered with emtricitabine/tenofovir disoproxil fumarate in human immunodeficiency virus (HIV)-1 infected, antiretroviral treatment-naïve adults) and study GS-US-216-105 (a phase II randomized, double-blinded study of the safety and efficacy of GS-9350-boosted atazanavir (ATV/GS-9350) compared to ritonavir boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment-naive adults). The RMP (version 2.0) is updated accordingly

15.3.4. Belimumab – BENLYSTA (CAP) - EMEA/H/C/002015/II/0040

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add information on the effect of Benlysta on vaccine responses in subjects with systemic lupus erythematosus (SLE) based on the results from study BEL115470 (HGS1006-C1117) to fulfil MEA 004.3. The RMP is updated accordingly

15.3.1. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0018/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Submission of two final study reports for non-clincial studies NCPK 278 and NCPK 293 to evaluate the potential pharmacodynamic and pharmacokinetic interactions between amiodarone and hepatitis C virus (HCV) direct acting antivirals (DAAs) including daclatasvir, in order to fulfil MEAs 015 and 016 . As a consequence the RMP is updated accordingly

15.3.2. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/II/0014

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the prevention of cardiovascular events, based on the final data of the cardiovascular safety phase III clinical trial EMPA-REG OUTCOME. As a consequence, section 4.1 of the SmPC is updated in order to add safety information on this study. The Package Leaflet is updated accordingly

15.3.3. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include the prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP (version 11.0) is updated accordingly

15.3.4. Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the paediatric population from 1 to 18 years of age for Ryzodeg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

15.3.5. Lumacaftor, ivacaftor – ORKAMBI (CAP) - EMEA/H/C/003954/II/0005/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final study reports for the following studies in order to address MEA 006: 1. Report L240: In vitro evaluation of the substrate and inhibitor potential of lumacaftor (VX-809) for breast cancer resistance protein and multidrug resistance protein 2. 2. Report L242: evaluation of the inhibition potential of VX-809 for uptakes transporters OAT1, OAT3, OCT1 and OCT2. 3. Report L239: In vitro drug-drug interaction studies of the sponsor's test article, VX-770. 4. Report L241: evaluation of the inhibition potential of VX-770 for uptake transporters OAT1, OAT3, OCT1 and OCT2. The RMP (version 2.1) is updated accordingly

15.3.6. Methylthioninium chloride – METHYLTHIONINIUM CHLORIDE PROVEBLUE (CAP) - EMEA/H/C/002108/II/0030/G

Applicant: Provepharm SAS

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 4.8 of the SmPC in order to include paresthesia, dysgeusia, syncope, presyncope, feeling of change in body temperature, chest discomfort, shoulder pain and limb discomfort based on data from two clinical studies. In addition, frequencies were added in the tabulated list of adverse reactions. The Package Leaflet is updated accordingly. The RMP (version 2.0) is updated accordingly

15.3.7. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0095

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section sections 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC based on the results of paediatric studies 101MS028 and 101MS328, in accordance with the paediatric investigation plan (EMEA-001095-PIP-12). The RMP (version 21) is updated accordingly

15.3.8. Nepafenac – NEVANAC (CAP) - EMEA/H/C/000818/II/0032

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include the 'reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients' for the 3 mg/ml strength based on data from the phase III studies C-12-067 and C-12-071. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to update the annexes in line with the latest QRD template. The RMP (version 7) is updated accordingly

15.3.9. Nintedanib – VARGATEF (CAP) - EMEA/H/C/002569/II/0009

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Submission of the final clinical study report for study 1199.120: an open label, dose escalation phase I study to evaluate the safety and tolerability of continuous twice-daily oral treatment of nintedanib in Japanese patients with hepatocellular carcinoma, to fulfil MEA 003. The RMP is updated accordingly. In addition, the MAH took the opportunity to update the RMP with the required updates requested in the outcome of EMEA/H/C/WS0766 variation

15.3.10. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0012

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL): - after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or - after at least two prior therapies in patients who are not candidates for ASCT. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet is updated accordingly. Furthermore, the product information is brought in line with the latest QRD template version 10.0. Moreover, the RMP (version 5.0) is updated accordingly

15.3.11. Ofatumumab – ARZERRA (CAP) - EMEA/H/C/001131/II/0045/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the combination of Arzerra with fludarabine and cyclophosphamide or in combination with bendamustine for the treatment of adult patients with relapsed chronic lymphocytic leukaemia (CLL). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 6.6 and 9 of the SmPC are updated.The Package Leaflet and the RMP (version 13) are updated accordingly

15.3.12. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0008/G

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2 and 5.2 of the SmPC with recommendations for patients with renal impairment based on the results of study D0816C00006 (MEA 006), that evaluated the influence of mild and moderate renal impairment on the pharmacokinetics of Olaparib. The Package Leaflet and RMP are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the product information in line with the latest QRD template version and to introduce minor corrections in the product information. Furthermore, a grouping of two type IB variations is submitted to revise the study milestones dates for the category 3 study D0816C00005 and category 1 study D0816C00002 in the RMP. The annex II has been amended accordingly

15.3.13. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0007

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the second line treatment of non-small cell lung cancer (NSCLC). As a consequence, sections 4.1, 4.2 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

15.3.14. Posaconazole – NOXAFIL (CAP) - EMEA/H/C/000610/II/0044

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.2 of the SmPC in order to strengthen the information about non-interchangeability of the oral formulations based on new reports of medication errors related to confusion between posaconazole tablets and oral suspension in prescribing. The Package Leaflet and the RMP are updated accordingly

15.3.15. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/II/0057

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate (MTX) in the SmPC for the subcutaneous formulation. As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Moreover, the RMP (version 18) is updated accordingly

15.3.16. Vandetanib – CAPRELSA (CAP) - EMEA/H/C/002315/II/0016

Applicant: AstraZeneca AB

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the treatment of paediatric population. As a consequence, sections 4.1, 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC are. The Package Leaflet is updated accordingly

15.3.17. Vismodegib – ERIVEDGE (CAP) - EMEA/H/C/002602/II/0025/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information in the product information after finalisation of study MO25616 (specific obligation (SOB) 013). Considering the fulfilment of the SOB, the MAH is also proposing the switch of the conditional marketing authorisation (MA) to a full MA not subject to specific obligations. Data from the same study also fulfilled the analysis required in MEA 005 regarding evaluation of the time for washout of vismodegib after treatment discontinuation and in MEA 008 regarding reporting of adverse events. The Package Leaflet and the RMP are updated accordingly. Furthermore, the MAH took the opportunity to update the RMP with regard to the results from non-clinical studies subject to variation EMEA/H/C/002602/II/21 and to propose the deletion of hyponatremia as an important potential risk in the RMP and as an adverse drug reatcion in the product information as discussed in the previous PSUR (PSUSA/00010140/201407)

15.3.18. Vorapaxar – ZONTIVITY (CAP) - EMEA/H/C/002814/II/0005

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: Extension of indication to include the treatment of patients with peripheral arterial disease (PAD) and as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of local representative in Luxembourg in the Package Leaflet. Furthermore, the product pnformation is brought in line with the latest QRD template (version 9.1). Moreover, the RMP (version 2.0) is updated accordingly

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

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

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

16.1. PSUR procedures including centrally authorised products only

16.1.1. Boceprevir – VICTRELIS (CAP) - PSUSA/00009081/201511

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.2. Cobicistat, darunavir – REZOLSTA (CAP) - PSUSA/00010315/201511

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.3. Dalbavancin – XYDALBA (CAP) - PSUSA/00010350/201511

Applicant: Durata Therapeutics International B.V.

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.4. Darifenacin – EMSELEX (CAP) - PSUSA/00000933/201510

Applicant: Merus Labs Luxco S.A.R.L.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.1. Erlotinib – TARCEVA (CAP) - PSUSA/00001255/201511

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.2. Fluticasone furoate, vilanterol – RELVAR ELLIPTA (CAP), REVINTY ELLIPTA (CAP) - PSUSA/00010099/201511

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.3. Follitropin alfa – BEMFOLA (CAP), GONAL-F (CAP), OVALEAP (CAP) - PSUSA/00001463/201510

Applicant: Finox Biotech AG (Bemfola), Merck Serono Europe Limited (Gonal-F), Teva B.V. (Ovaleap)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.4. Follitropin alfa, lutropin alfa – PERGOVERIS (CAP) - PSUSA/00001464/201510

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.5. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - PSUSA/00009175/201511 (with RMP)

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.1. Lidocaine, prilocaine – FORTACIN (CAP) - PSUSA/00010110/201511

Applicant: Plethora Solutions Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.2. Mercaptamine – CYSTAGON (CAP), PROCYSBI (CAP) - PSUSA/00001987/201510

Applicant: Orphan Europe S.A.R.L. (Cystagon), Raptor Pharmaceuticals Europe BV (Procysbi)

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.3. Metformin, saxagliptin – KOMBOGLYZE (CAP) - PSUSA/00002686/201511

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.4. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - PSUSA/00010296/201511 (with RMP)

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.1. Pixantrone – PIXUVRI (CAP) - PSUSA/00009261/201511

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.2. Radium Ra^{223} dichloride – XOFIGO (CAP) - PSUSA/00010132/201511

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.3. Rituximab – MABTHERA (CAP) - PSUSA/00002652/201511

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.4. Rotavirus vaccine, live, oral, pentavalent – ROTATEQ (CAP) - PSUSA/00002666/201511 (with RMP)

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.5. Sapropterin – KUVAN (CAP) - PSUSA/00002683/201512 (with RMP)

Applicant: BioMarin International Limited

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.1. Stiripentol – DIACOMIT (CAP) - PSUSA/00002789/201511

Applicant: Biocodex

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Tilmanocept – LYMPHOSEEK (CAP) - PSUSA/00010313/201511

Applicant: Navidea Biopharmaceuticals Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.3. Tolvaptan – JINARC (CAP) - PSUSA/00010395/201511

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

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. Acetylsalicylic acid, bisoprolol (NAP) - PSUSA/00010287/201511

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.1. Artemether, lumefantrin (dispersible tablet) (NAP) - PSUSA/00009060/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.2. Azelastine, fluticasone (NAP) - PSUSA/00010067/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. Bromocriptine (NAP) - PSUSA/00000438/201510

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.4. Ceftazidime (NAP) - PSUSA/00000608/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.5. Clindamycin (NAP) - PSUSA/00000795/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.1. Human coagulation factor VIII, human von Willebrand factor (NAP) - PSUSA/00001621/201510

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.1. Letrozole (NAP) - PSUSA/00001842/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.2. Meningococcal group c polysaccharide conjugate vaccine (NAP) - PSUSA/00001971/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.1. Milrinone (NAP) - PSUSA/00002064/201510

Applicant: various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Paraffin liquid (NAP) - PSUSA/00009251/201510

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

16.3.1. Piretanide (NAP) - PSUSA/00002433/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.1. Tetrabenazine (NAP) - PSUSA/00002911/201510

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Trametinib – MEKINIST (CAP) - EMEA/H/C/002643/MEA 002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Follow-up from PSUSA/00010262/201511: submission of the second annual report for cardiomyopathy-related adverse reactions

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)[38]

17.1.1. Alipogene tiparvovec – GLYBERA (CAP) - EMEA/H/C/PSP/0046

Applicant: UniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study REG-uQ-Glyb-001: a lipoprotein lipase deficiency (LPLD) registry: observational longitudinal pharmacoepidemiologic study in LPLD patients, either treated or not treated with alipogene tiparvovec

17.1.2. Cholic acid– KOLBAM (CAP) - EMEA/H/C/PSP/0017.1

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

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

Scope: Revised PASS protocol for a patient registry to monitor the long term safety and efficacy in patients treated with cholic acid

17.1.3. Dexamfetamine (NAP) - EMEA/H/N/PSP/0018.2

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG.

PRAC Rapporteur: Julie Williams

Scope: Revised PASS protocol to evaluate the long-term safety profile of dexamfetamine in children with attention deficit hyperactivity disorder (ADHD), specifically targeting key issues such as cardiovascular events, growth and psychiatric related adverse events

17.1.4. Domperidone (NAP) - EMEA/H/N/PSP/j/0031.1

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Claire Ferard

Scope: Revised PASS protocol for a drug utilisation study on domperidone use in Europe using databases to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the changes in the product information and the distribution of a DHPC. The secondary objective of the study is to characterise the extent to which domperidone is prescribed for conditions that are not labelled

17.1.1. Levonorgestrel (NAP) - EMEA/H/N/PSP/J/0045

Applicant: Bayer Pharma AG, various
PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised PASS protocol for study EURAS-LCS12: a European active surveillance study of LCS-12, an intra-uterine device (IUD) for Jaydess and Luadei (levonorgestrel) to assess among new users the risks of certain events associated with the use of LCS-12 compared with established IUDs (e.g. Mirena, copper IUDs) during standard clinical practice and to describe drug utilisation patterns

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

17.2.1. Insulin detemir – LEVEMIR (CAP) - EMEA/H/C/000528/MEA/045.5

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: Revised PASS protocol for diabetes pregnancy registry (NN304-4016)

17.2.2. Insulin human – INSUMAN (CAP) - EMEA/H/C/000201/MEA/047.2

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 047.1 [PASS protocol for study HUBIN-C-06380, a prospective cohort study organised as exposure registry] as per request for supplementary information adopted in September 2015

[39] 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

17.2.3. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/006.2

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: MAH's responses to MEA 006.1 [revised protocol for naloxegol observational safety study in patients taking opioids for non-cancer pain (study D2288R00084)] as per request for supplementary information adopted in November 2015

17.2.4. Necitumumab – PORTRAZZA (CAP) - EMEA/H/C/003886/MEA/001

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for a physician/oncologist knowledge survey to assess physicians'/oncologists' understanding of the key conditions for the safe use of necitumumab

17.2.5. Necitumumab – PORTRAZZA (CAP) - EMEA/H/C/003886/MEA/002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: 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

17.2.6. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/MEA/021.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 021 [protocol for study GS-EU-337-2030: an observational, cross-sectional post-authorisation safety study to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information adopted in January 2016

17.2.7. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/013.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 013.1 [revised protocol for study GS-EU-337-1820: a prospective observational drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C (HCV)/human immunodeficiency virus (HIV) co-infection] asper request for supplementary information adopted in January 2016

17.2.8. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/014.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: MAH's responses to MEA 014 [protocol for study GS-EU-337-2030: an observational, cross-sectional PASS to assess healthcare providers awareness of risks related to sofosbuvir

and ledipasvir/sofosbuvir (LDV/SOF)] as per request for supplementary information as adopted in January 2016

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

17.3.1. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0068

Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final results for the drug utilisation study Eurovision 2. The RMP has been amended to refine the additional risk minimisation measures in line with the findings of the study

17.3.2. Fluticasone furoate – AVAMYS (CAP) - EMEA/H/C/000770/II/0030/G

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final clinical study report for post authorisation safety study (PASS) 201077: a retrospective case-control studyof rare adverse events associated with intranasal steroids. In addition, submission of a revised RMP (version 11) to include cataracts and glaucoma as identified risks, following the recommendation of PSUSA/00009154/201504 adopted in December 2015

17.3.1. Indacaterol – HIROBRIZ BREEZHALER (CAP) - EMEA/H/C/001211/WS/0944; ONBREZ BREEZHALER (CAP) - EMEA/H/C/001114/WS/0944; OSLIF BREEZHALER (CAP) - EMEA/H/C/001210/WS/0944

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Submission of the final study report for study US PASS QAB149B2432 (CQAB149BS232861) to fulfil MEA 017/MEA 015/MEA 015 for Onbrez Breezhaler, Hirobriz Breezhaler and Oslif Breezhaler respectively. In addition, the RMPs (version 9.0) are also updated to reflect results from this completed study and to remove it from the ongoing pharmacovigilance activities

17.3.2. Insulin glargine – LANTUS (CAP) - EMEA/H/C/000284/II/0105

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study, a study in patients with type 1 ortype 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037

17.3.3. Insulin glulisine – APIDRA (CAP) - EMEA/H/C/000557/II/0066

Applicant: Sanofi-aventis Deutschland GmbH

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

PRAC Rapporteur: Julie Williams

Scope: Submission of the final clinical study report for a PASS: UK SoloStar differentiation study, a study in patients with type 1 ortype 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar pens containing different types of insulin with the current and new labels. This submission addresses MEA 037

17.3.1. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0062

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final clinical study report for study V59_54OB, a post-licensure observational safety surveillance study of Menveo vaccination in children 2 through 10 years of age, in order to update the safety information of Menveo in subjects aged 2-10 years of age to fulfil MEA 024

17.4. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[41]

17.4.1. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/005.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 005.5 [six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016

17.4.2. Canagliflozin – INVOKANA (CAP) - EMEA/H/C/002649/MEA/006.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 006.1 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016

17.4.3. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/004.6

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 004.5 [six-monthly status report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016

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

17.4.4. Canagliflozin, metformin – VOKANAMET (CAP) - EMEA/H/C/002656/MEA/005.2

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 005.1 [first status report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity], as per the request for supplementary information adopted in February 2016

17.4.5. Estrogens conjugated, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA/002.3

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: First interim analysis report for an US PASS: active surveillance of conjugated estrogens (CE)/bazedoxifene acetate (BZA) using US healthcare data (study B2311060, category 3 study)

17.4.6. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/004.5

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Interim results of the enhanced safety surveillance study D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age

17.4.7. Micafungin – MYCAMINE (CAP) - EMEA/H/C/000734/MEA/013.2

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 013.1 [annual interim report from an observational database-assisted comparative cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma (protocol number: ISN 9463-CL-140): a multicentre cohort study of the short and long-term safety of micafungin and Other parenteral antifungal agents (MYCOS)] as per request for supplementary information adopted in December 2015

17.4.8. Temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/LEG/031.4

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to LEG 031.3 [interim results from Japanese non-interventional studies 3066K5-4406 (Torisel 25 mg for intravenous drip infusion special investigation - all patients survey) and B1771016 (Torisel 25 mg for intravenous drip infusion special investigation - survey on long term use)] as per request for supplementary information adopted in January 2016

17.5. Others

17.5.1. Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) – PANDEMRIX[42] - EMEA/H/C/000832/MEA 122.1

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 0122 [final study report for PASS study EPI-FLU H1N1-014 VS: an observational retrospective database analysis to estimate the risk of multiple sclerosis following vaccination with Arepanrix in Manitoba, Canada] as per request for supplementary information adopted in March 2016

17.6. New Scientific Advice

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

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

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

18.1. Annual reassessments of the marketing authorisation

18.1.1. Amifampridine – FIRDAPSE (CAP) - EMEA/H/C/001032/S/0040 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/R/0022 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

[42] Marketing Authorisation expired on 13 August 2015

18.3. Renewals of the marketing authorisation

18.3.1. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/R/0023 (without RMP)

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.2. Desloratadine – DASSELTA (CAP) - EMEA/H/C/002310/R/0012 (without RMP)

Applicant: Krka, d.d., Novo mesto

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.3. Desloratadine – DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/R/0015 (without RMP)

Applicant: Ratiopharm GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.4. Desloratadine – DESLORATADINE TEVA (CAP) - EMEA/H/C/002419/R/0014 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.5. Fidaxomycin – DIFICLIR (CAP) - EMEA/H/C/002087/R/0026 (with RMP)

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.6. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/R/0020 (without RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: 5-year renewal of the marketing authorisation

18.3.7. Levetiracetam – LEVETIRACETAM ACTAVIS GROUP (CAP) - EMEA/H/C/002305/R/0012 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

18.3.8. Ranibizumab – LUCENTIS (CAP) - EMEA/H/C/000715/R/0062 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

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 6-9 June 2016 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
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	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
Nectaroula Cooper	Member	Cyprus	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
Kimmo Jaakkola	Alternate	Finland	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
Claire Ferard	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
Leonidas Klironomos	Member	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	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
Miroslava Matíková	Alternate	Slovakia	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
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
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Member	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Martin Erik Nyeland	Observer - in	Denmark	No	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	person*		restrictions applicable to this meeting	
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Alexandre Moreau	Expert - in person*	France	No interests declared	Full involvement
Clemens Mittmann	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Amany N. El-Gazayerly	Expert - in person*	Netherlands	No interests declared	Full involvement
Fakhredin Sayed Tabatabaei	Expert - in person*	Netherlands	No interests declared	Full involvement
Sophia Venzke	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Eirik Hagtvet	Expert - in person*	Norway	No interests declared	Full involvement
Helga Haugom Olsen	Expert - in person*	Norway	No interests declared	Full involvement
Joanna Plichta	Expert - via telephone*	Poland	No interests declared	Full involvement
Jonas Bergh	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Annika Ekbom Schnell	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Hanna Norek	Observer - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Patrick Batty	Expert - in person*	United Kingdom	No interests declared	Full involvement
Inga Bellahn	Expert - in person*	United Kingdom	No interests declared	Full involvement
Philip Bryan	Expert - in	United Kingdom	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	
Mattia Calissano	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
John Clements	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Claire Davies	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jennifer Matthissen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Maria Beatrice Panico	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Nicola Parkinson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Catherine Tregunno	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, 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/