4 October 2018
EMA/PRAC/675727/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 03-06 September 2018

Chair: Sabine Straus – Vice-Chair: vacant

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

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

The new Chairperson, Sabine Straus, opened the 03-06 September 2018 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Rhea Fitzgerald, replacing Almath Spooner as the new member for Ireland, leaving the position of alternate vacant for the time being. Menno van der Elst was also welcomed as the new member for the Netherlands, replacing Sabine Straus and leaving the position of alternate vacant for the time being. In addition, the Chair welcomed Eva Segovia, replacing Dolores Montero Corominas, as the new member for Spain and Maria del Pilar Rayon as the new alternate for Spain replacing Eva Segovia in this role. Moreover, the Chair welcomed Gabriela Jazbec, replacing Milena Radoha-Bergoč, as the new member for Slovenia and Jasmina Klopcic as the new alternate for Slovenia replacing Gabriela Jazbec in this role. Furthermore, the Chair welcomed Adrien Inoubli, replacing Caroline Laborde, as the new alternate for France. Finally, it was noted that Andreia Rulea is the new alternate for Romania replacing Roxana Dondera.

1.2. Agenda of the meeting on 03-06 September 2018

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 09-12 July 2018

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 09-12 July 2018 were published on the EMA website on 1 October 2018 (EMA/PRAC/576790/2018).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures[1]

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

[1] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[2] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

4.1.1. Fingolimod - GILENYA (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of autoimmune haemolytic anaemia

EPITT 19260 – New signal

Lead Member State(s): FR

Background

Gilenya is a centrally authorised medicine containing fingolimod, a selective immunosuppressant. It is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy and for adult patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The exposure for Gilenya (fingolimod) is estimated to have been approximately 536,872 patient-years (PTY) worldwide, in the period from first authorisation in 2010 to 2018.

During routine signal detection activities, a signal of autoimmune haemolytic anaemia was identified by EMA, based on 16 cases retrieved from EudraVigilance with the MedDRA PT[3] autoimmune haemolytic anaemia. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the PRAC agreed that Novartis Europharm Limited, the MAH for Gilenya (fingolimod) should submit in the next PSUR (data lock point (DLP): 28/02/2019), a cumulative review of the signal with a discussion on the need for any potential amendment to the product information and/ or the risk management plan as well as an adequate proposal for the changes to the relevant sections within this discussion.

Summary of recommendation(s)

- The MAH for Gilenya (fingolimod) should submit to EMA within the next PSUR, unless new evidence emerges warranting a more urgent action, a cumulative review of all cases of the MedDRA SMQ[4] (narrow) 'haemolytic disorders' (with a particular focus on cases of autoimmune haemolytic anaemia) associated with Gilenya (fingolimod), including a discussion on the plausible biological mechanism and the possible risk factors. In addition, the MAH should provide a discussion on the need for any potential amendment to the product information and/or the RMP with a corresponding proposal.

  See also 6.1.4.

[3] Medical dictionary for regulatory activities – Preferred term
[4] Medical dictionary for regulatory activities – Standardised MedDRA query

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Clomipramine (NAP); Serotonin and noradrenaline reuptake inhibitors (SNRI)[5]: desvenlafaxine (NAP); duloxetine - ARICLAIM (CAP), CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP); milnacipran (NAP); venlafaxine (NAP); Selective serotonin reuptake inhibitors (SSRI)[6]: citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP); Vortioxetine – BRINTELLIX (CAP)

Applicant(s): Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Generics UK Limited (Duloxetine Mylan), H. Lundbeck A/S (Brintellix), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of persistent sexual dysfunction after drug withdrawal

EPITT 19277 – New signal

Background

Clomipramine is a non-selective monoamine reuptake inhibitor indicated, among others, for the treatment of major depressive disorder. Desvenlafaxine, duloxetine, milnacipran and venlafaxine are serotonin and noradrenaline reuptake inhibitors (SNRIs) indicated, among others, for the treatment of major depressive disorder. Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are selective serotonin reuptake inhibitors (SSRIs) indicated, among others, for the treatment of major depressive disorder. Brintellix is a centrally authorised product containing vortioxetine, a psychoanaleptic antidepressant. It is indicated for the treatment of major depressive disorders in adults.

Cymbalta and Yentreve, centrally authorised medicines containing duloxetine, are estimated to have been used by approximately 91,636,000 patients worldwide (all indications) in the period from first authorisations in 2004 to 2017. Milnacipran capsule for major depressive episodes[7] is estimated to have been used by more than 8,611,639 patients (corresponding to 15,296,991 patients-months) worldwide in the period from first authorisation in 1966 to 2018. Escitalopram (all indication) is estimated[8] to have been used by approximately 402,748,747 patients worldwide in the period from first authorisation in 2001 to 2016. The exposure for fluvoxamine (all indications) is estimated[9] to have been approximately 1,560,498 patient treatment years worldwide in the period from first authorisation in 1983 to 2017. Paroxetine (all indications) is estimated[10] to have been used by more than 400 million patients worldwide in the period from first authorisation in 1990 to 2017. The exposure to sertraline (all indications) is estimated[11] to have been approximately 146,798,100 patient-years worldwide in the period from first authorisation in 1990 to 2017. The exposure for

[5] Indicated in the treatment of major depressive disorder (MDD)
[6] Indicated in the treatment of major depressive disorder (MDD)
[7] Ixel. Joncia, Dalcipran, Tivanyl, Savella, Toledomin, Milnacipran Pierre Fabre
[8] By H. Lundbeck A/S
[9] By Mylan
[10] By GlaxoSmithKline Research & development
[11] By Pfizer

Brintellix (vortioxetine) is estimated to have been approximately 2,429,103 patient-years worldwide in the period from first authorisation in 2013 to 2017. The exposure for fluoxetine (all indications) is estimated to have been approximately 121,620,000 patient-years worldwide in the period from first authorisation in 1986 to 2017.

Following some ongoing procedures, where some EU Member States have reviewed information on persistent sexual dysfunction for SSRIs and SNRIs, including spontaneous data in EudraVigilance (EV), recent literature and a petition from a group of professors, psychiatrists and related healthcare professionals (HCPs) concerning persistent sexual disorders with SSRIs and SNRIs, where authors refer to literature cases of genital anaesthesia, persistent genital arousal disorder (PGAD) and post-SSRI sexual dysfunctions (PSSD) and postulate changes in product information, risk minimisation measures taken by MAHs and communication to both HCPs and patients, a signal of persistent sexual dysfunction after drug withdrawal was identified by EMA. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available data, including a publication in the International Journal of Risk & Safety in Medicine by *Healy D. et al.*[12] and 574 case reports retrieved for duloxetine in EV with relevant MedDRA HLT[13], the PRAC concluded that the signal merits further investigation.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

Summary of recommendation(s)

- The Lead Member States (LMS)/Rapporteurs for the concerned active substances will review the literature referenced in the above-mentioned petition received by the Agency. In addition, EMA will perform literature reviews, EV data analysis and will explore the feasibility for a pharmacoepidemiological study. Finally, EMA in collaboration with the LMS/Rapporteurs will elaborate on appropriate case definitions for the sexual dysfunction disorders adverse drug reactions (ADRs), using read codes and MedDRA terms, to facilitate further assessments.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Rivaroxaban – XARELTO (CAP)

Applicant(s): Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of premature ending of the GALILEO[14] study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement (TAVR)

EPITT 19294 – New signal

[12] Healy D, Le Noury J, Mangin D. Enduring Sexual Dysfunction after Treatment with Antidepressants, 5α-Reductase Inhibitors and Isotretinoin: 300 Cases. Int. J. Risk. Saf. Med. 2018. doi:10.3233/JRS-180744
[13] Medical dictionary for regulatory activities – High level term
[14] A global multicentre, open-label, randomised, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes

Lead Member State(s): SE

Background

Xarelto is a centrally authorised medicine containing rivaroxaban, a direct factor Xa inhibitor. It is indicated under certain conditions for the prevention of venous thromboembolism (VTE) in adults undergoing elective hip/knee replacement surgery, for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults, and for the prevention of atherothrombotic events in adults after an acute coronary syndrome (ACS) with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) or with ASA plus clopidogrel/ticlopidine.

The exposure for Xarelto (rivaroxaban) is estimated to have been approximately 5.3 million patient-years worldwide, in the period from first authorisation in 2008 to 2017.

Following the notification to EMA of the premature termination of the GALILEO clinical trial (a global multicentre, open-label, randomised, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR)[15] to optimize clinical outcomes) by the study sponsor, a signal was identified by the EMA. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the preliminary results from the early terminated GALILEO study where rivaroxaban was studied in patients after TAVR, and which suggest an increase in all-cause mortality and thromboembolic and bleeding disorders, the PRAC agreed that the MAH of Xarelto (rivaroxaban) and sponsor of the GALILEO study should submit an in-depth data analysis of the signal. It is acknowledged that further data collection and analyses are required to fully evaluate this safety concern, which will take several months while awaiting further study results.

Summary of recommendation(s)

- The MAH for Xarelto (rivaroxaban)/sponsor of the GALILEO study should submit to EMA, within 7 months, an in-depth analysis of the signal, including (but not limited to) answers to the adopted list of questions. This includes that the MAH should, e.g. based on further analyses of GALILEO, discuss the impact of age, severity of cardiovascular disease, comorbidity, and general frailty on the adverse outcome. This should also be considered in relation to patients being eligible for approved indications. The MAH should also review the data from the overall rivaroxaban study program and spontaneous reporting, focusing on thrombotic and thromboembolic events and deaths in patients >75 years of age compared with younger age groups, and in relation to relevant comorbidity. In addition, the MAH should comment on the apparent pattern with more valve thromboses in the control arm, but more primary ischemic stroke in the rivaroxaban arm. It is considered that a mechanistic discussion is warranted regarding thrombus stability in relation to treatment strategy. Furthermore, the MAH should liaise with the sponsor/investigators of the RIVER[16] study, to try to obtain as much

[15] Non-approved use of rivaroxaban
[16] A phase 2, randomized, open label, non-inferiority clinical trial to explore the safety and efficacy of rivaroxaban compared with vitamin K antagonism in patients with atrial fibrillation with bioprosthetic mitral valves. NCT02303795

information as possible in relation to the results of this study. Additionally, the MAH should assess the need for further actions in relation to this issue, including the potential consequences for the medicinal product.

- Given the severity of the adverse effects, the unknown extent of use in the TAVR patient population (an unapproved use), and the time it will take to finalise the analyses of GALILEO including awaiting more mature data, the PRAC agreed to communicate the results of the trial via a direct healthcare professional communication (DHPC) to relevant healthcare professionals already at this stage. Therefore, the PRAC agreed on the content of a DHPC and communication plan for further consideration at CHMP.
- The PRAC will further consider this issue once additional data, including the final results of the GALILEO trial/further analysis by the GALILEO investigators, become available.

4.3. Signals follow-up and prioritisation

4.3.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/SDA/008

Applicant(s): Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of cytomegalovirus (CMV) infection

EPITT 19193 – Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

The MAH replied to the request for information on the signal of cytomegalovirus (CMV) infection and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance, the literature, clinical trials and the cumulative review by Sanofi, the MAH of Lemtrada (alemtuzumab), the PRAC agreed that the MAH should submit a variation with a view to amending the product information to include a special warning and precaution for use following the report of cytomegalovirus (CMV) infections including cases of CMV reactivation in Lemtrada (alemtuzumab)-treated patients and to add cytomegalovirus infection as an undesirable effect with a frequency 'uncommon'.

Summary of recommendation(s)

- The MAH for Lemtrada (alemtuzumab) should submit to EMA, within 60 days, a variation to amend the product information[17].

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.2. Dimethyl fumarate – TECFIDERA (CAP) - EMEA/H/C/002601/SDA/019

Applicant(s): Biogen Idec Ltd

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

PRAC Rapporteur: Martin Huber

Scope: Signal of immune thrombocytopenic purpura and thrombocytopenia

EPITT 19192 – Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

The MAH replied to the request for information on the signal of immune thrombocytopenic purpura and thrombocytopenia and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature for an association between thrombocytopenia and dimethyl fumarate indicated for the treatment of multiple sclerosis, the PRAC agreed that Biogen Idec Ltd, the MAH of Tecfidera (dimethyl fumarate) should submit a variation with a view to amending the Tecfidera (dimethyl fumarate) product information to add thrombocytopenia as an undesirable effect with a frequency 'uncommon'. Furthermore, the PRAC agreed that the likelihood of a causal relationship between immune thrombocytopenic purpura and dimethyl fumarate indicated for the treatment of multiple sclerosis is not sufficiently strong to warrant changes in the product information at this stage. However, the MAH should continue to monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The MAH for Tecfidera (dimethyl fumarate) should submit to EMA, within 60 days, a variation for amending the product information[18]. In addition, the MAH for Tecfidera (dimethyl fumarate) should continue to monitor the occurrence of immune thrombocytopenic purpura events as part of routine safety surveillance.

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.3. Duloxetine – CYMBALTA (CAP) - EMEA/H/C/000572/SDA/047, DULOXETINE LILLY (CAP) - EMEA/H/C/004000/SDA/004, DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP) - EMEA/H/C/000573/SDA/048, YENTREVE (CAP) - EMEA/H/C/000545/SDA/043; NAP

Applicant(s): Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Mylan S.A.S. (Duloxetine Mylan), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of interstitial lung disease (ILD)

EPITT 19175 – Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

The MAH replied to the request for information on the signal of interstitial lung disease (ILD) and the responses were assessed by the Rapporteur.

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

Discussion

Having considered the available evidence in EudraVigilance and in the literature for an association of duloxetine with interstitial lung disease, the PRAC agreed that the MAH(s) of duloxetine-containing medicinal products should submit a variation with a view to amending the product information to include interstitial lung disease and eosinophilic pneumonia as undesirable effects with a frequency 'rare', as estimated based on placebo-controlled trials and on post-marketing surveillance reported adverse reactions (not observed in placebo-controlled clinical trials) respectively.

Summary of recommendation(s)

- The MAH for duloxetine-containing medicinal products should submit to EMA or to the relevant national competent authorities of the MSs, within 60 days, a variation for amending the product information[19].

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

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

PRAC Rapporteur: Martin Huber

Scope: Signal of aortic aneurysm and dissection

EPITT 18651 – Follow-up to July 2018

Background

For background information, see PRAC minutes July 2018.

The MAHs replied to the request for information on the signal of aortic aneurysm and dissection and the responses were assessed by the Rapporteur.

Discussion

Having considered the evidence from epidemiological (*Lee et al.* 2015[20], *Daneman et al.* 2015[21], *Pasternak et al.* 2018[22]) and non-clinical studies (*LeMaire et al.* 2018[23]), and the responses from the MAHs of fluoroquinolones-containing medicines, the PRAC agreed that the MAHs of fluoroquinolones-containing medicines for systemic and inhaled use should submit a variation with a view to amending the product information to include a special warning and precautions for use following the report of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population in

[19] Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly
[20] Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med. 2015 Nov;175(11):1839-47
[21] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open. 2015 Nov 18; 5(11):e010077
[22] Pasternak B, Inghammar M and Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018; 360: k678
[23] LeMaire SA, Zhang L, Luo W, Ren P, Azares AR, Wang Y, Zhang C, Coselli JS, Shen YH. Effect of ciprofloxacin on susceptibility to aortic dissection and rupture in mice. JAMA Surg. 2018 Jul 25:e181804. [Epub ahead of print]

epidemiologic studies. In addition, the MAHs should also collaboratively distribute a single direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC.

Summary of recommendation(s)

- The MAHs for fluoroquinolone-containing medicines for systemic and inhaled use should submit to the EMA or the relevant national competent authorities of the MSs as applicable, within 90 days, a variation for amending the product information[24].
- In addition, the MAHs of fluoroquinolone-containing medicines should also collaboratively distribute a single DHPC according to the text and communication plan agreed with the PRAC. The finalisation and distribution of the DHPC should be coordinated by the MAH Sanofi.

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.5. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)

Applicant(s): Actavis Group PTC ehf (Actelsar HCT), Bayer Pharma AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International (MicardisPlus), Krka, d.d. (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT), Sanofi-aventis groupe (Irbesartan Hydrochlorothiazide Zentiva, Karvezide), Sanofi Clir SNC (CoAprovel), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva), various

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of skin cancer

Action: For adoption of PRAC recommendation

EPITT 19138 – Follow-up to July 2018

Background

For background information, see PRAC minutes July 2018.

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

Discussion

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered there was a biologically plausible mechanistic model supporting the increased risk of non-melanoma skin cancer (NMSC) following higher cumulative doses of hydrochlorothiazide (HCTZ). Therefore, the PRAC agreed that the MAHs for HCTZ-containing

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

products should submit a variation with a view to amending the product information to include special warnings and precautions for use following the observation of an increased risk of NMSC (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) with increasing cumulative dose of HCTZ exposure in two epidemiological studies based on the Danish national cancer registry, to include NMSC (BCC and SCC) as an undesirable effect with a frequency not known, as well as to add data from epidemiological studies supporting the observed cumulative dose-dependent association between HCTZ and NMSC. Additionally, PRAC considered that a direct healthcare professional communication (DHPC) should be distributed at the national level in the EU. Therefore, the originator MAHs for HCTZ-containing medicinal products are to submit a single DHPC. The PRAC considered that, since there are several medicinal products with the same active substance/combination of substances for which a DHPC is to be issued, a single consistent message should be delivered.

Summary of recommendation(s)

- The MAHs for HCTZ-containing medicinal products should submit to EMA or to the relevant national competent authorities of the MSs as appropriate, within 60 days, a variation for amending the product information[25].
- In addition, the originator MAHs of HTCZ-containing medicines should collaboratively distribute a single DHPC. A single consistent message should be delivered considering that there are several medicinal products with the same active substance/combination of substances for which a DHPC is to be issued. The PRAC agreed on the content of the DHPC together with a communication plan.

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.6. Ipilimumab – YERVOY (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of cytomegalovirus (CMV) gastrointestinal infection

EPITT 19207 – Follow-up to May 2018

Background

For background information, see PRAC minutes May 2018.

The MAH replied to the request for information on the signal of cytomegalovirus (CMV) gastrointestinal infection and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that the MAH of Yervoy (ipilimumab) should submit a variation with a view to amending the product information to include special warnings and precautions for use further to the reports of post-marketing cases of CMV infection/reactivation in patients with corticosteroid-refractory immune-related colitis.

[25] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is to be updated accordingly

Summary of recommendation(s)

- The MAH for Yervoy (ipilimumab) should submit to EMA, within 60 days, a variation for amending the product information[26].

For the full PRAC recommendation, see EMA/PRAC/595691/2018 published on 01/10/2018 on the EMA website.

4.3.7. Olanzapine – ZALASTA (CAP) - EMEA/H/C/000792/SDA/006, ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/028, ZYPREXA (CAP) - EMEA/H/C/000115/SDA/049, ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/042; NAP

Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Krka d.d. (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of somnambulism

EPITT 19202 – Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

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

Discussion

Having considered the available evidence from the cumulative review provided by Eli Lilly Nederland B.V., the MAH for Zyprexa (olanzapine), the PRAC agreed that given the wide use of olanzapine, the fact that epidemiology data have shown that parasomnias are relatively common in the target population as well as that in the reviewed cases a definite causality could not be attributed exclusively to olanzapine due to other confounding factors that could have influenced on the risk of parasomnias, the evidence is not sufficiently robust to warrant changes in the product information at this stage. Therefore, no further action is deemed warranted at this point in time. However, the MAHs of olanzapine-containing products should continue to monitor these events as part of routine safety surveillance and present the review in the next PSUR.

Summary of recommendation(s)

- The PRAC considered that no further action was deemed warranted at this point in time. Nevertheless, the MAHs of olanzapine-containing products should continue to monitor the events of somnambulism as part of routine safety surveillance and present the review in the next PSUR.

4.3.8. Sildenafil - GRANPIDAM (CAP), MYSILDECARD (CAP), REVATIO (CAP) – EMEA/H/C/000638/SDA/050, SILDENAFIL ACTAVIS (CAP), SILDENAFIL RATIOPHARM (CAP), SILDENAFIL TEVA (CAP), VIAGRA (CAP), VIZARSIN (CAP); NAP

Applicant(s): Pfizer Limited (Revatio, Viagra), Accord Healthcare (Granpidam), Mylan S.A.S

[26] Update of SmPC section 4.4

(Mysildecard), Actavis Group PTC (Sildenafil Actavis), Ratiopharm GmbH (Sildenafil Ratiopharm), Teva B.V. (Sildenafil Teva), Krka, d.d., Novo mesto (Vizarsin); various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction

EPITT 19287 – Follow-up to July 2018

Background

For background information, see PRAC minutes July 2018.

The MAH(s) replied to the request for information on the signal of pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction, and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available evidence from the preliminary data from the STRIDER trials, including the Dutch-STRIDER trial, as well as the supplementary information provided by the MAH, and noted that while further data were necessary to allow consideration in the broader context of the available data, healthcare professionals should be informed to avoid the use of sildenafil for the unapproved use in intrauterine growth restriction.

Summary of recommendation(s)

- The PRAC agreed that Pfizer, the originator MAH for Revatio/Viagra (sildenafil) should distribute a direct healthcare professional communication (DHPC). The PRAC agreed on the content of the DHPC together with a communication plan to be further reviewed by CHMP.
- The PRAC will further consider this issue once additional data, including the final results of the STRIDER trial/further analysis by the STRIDER investigators, become available.

4.3.9. Sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/SDA/037, RISTABEN (CAP) - EMEA/H/C/001234/SDA/015, TESAVEL (CAP) - EMEA/H/C/000910/SDA/031, XELEVIA (CAP) - EMEA/H/C/000762/SDA/036; sitagliptin, metformin hydrochloride – JANUMET (CAP) - EMEA/H/C/000861/SDA/019, EFFICIB (CAP) - EMEA/H/C/000896/SDA/019, RISTFOR (CAP) - EMEA/H/C/001235/SDA/015, VELMETIA (CAP) - EMEA/H/C/000862/SDA/019 Angiotensin-converting-enzyme (ACE)-inhibitors: benazepril (NAP); captopril (NAP); cilazapril (NAP); delapril (NAP); enalapril (NAP); fosinopril (NAP); imidapril (NAP); lisinopril (NAP); moexipril (NAP); perindopril (NAP); quinapril (NAP); ramipril (NAP); spirapril (NAP); trandolapril (NAP); zofenopril (NAP); zofenopril, hydrochlorothiazide (NAP)

Applicant(s): Merck Sharp & Dohme B.V., various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of potential drug interaction between sitagliptin and angiotensin-converting-enzyme (ACE)-inhibitors leading to an increased risk of angioedema

EPITT 17608 – Follow-up to April 2018

Background

For background information, see PRAC minutes April 2018.

The MAH replied to the request for information on the signal of potential drug interaction between sitagliptin and angiotensin-converting-enzyme-inhibitors (ACEi) leading to an increased risk of angioedema and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review provided by the MAH regarding the potential interaction between sitagliptin and ACEi, the fact that insufficient evidence was found indicating an increase in frequency of occurrence of angioedema with this combination therapy and taking into account that angioedema is included as an undesirable effect in the product information of both classes of products, the PRAC agreed that this signal could be closed.

Additionally, as angioedema is an identified risk in the RMP of sitagliptin-containing products, new information regarding this risk will be presented in upcoming PSURs.

Summary of recommendation(s)

- The PRAC agreed that this signal could be closed.
- The MAH for the sitagliptin-containing products should continue to monitor these events as part of routine safety surveillance.

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).

See also Annex I 15.1.

5.1.1. Apalutamide - EMEA/H/C/004452

Scope: Treatment of non-metastatic castration resistant prostate cancer (NM CRPC)

5.1.2. Fexinidazole - Art 58[27] - EMEA/H/W/002320

Scope: Treatment of human African trypanosomiasis (HAT)

For further background, see PRAC minutes April 2018.

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

5.1.3. Macimorelin - EMEA/H/C/004660

Scope: Diagnosis of adult growth hormone deficiency (AGHD)

5.1.4. Romosozumab - EMEA/H/C/004465

Scope: Treatment of osteoporosis

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

See also Annex I 15.2.

5.2.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0182

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 14.0) in order to include a review of the currently specified safety concerns and recently assessed safety concerns and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

Background

Adalimumab is a human monoclonal antibody that binds specifically to tumour necrosis factor (TNF) and inhibits the biological function of TNF. It is indicated, as Humira, for the treatment of rheumatoid arthritis, of juvenile idiopathic arthritis, of axial spondyloarthritis, of psoriatic arthritis, of psoriasis, of paediatric plaque psoriasis, of hidradenitis suppurativa (HS), of adolescent HS, of Crohn's disease, of paediatric Crohn's disease, of ulcerative colitis, of uveitis, and for the treatment of paediatric uveitis under certain conditions.

The PRAC is evaluating a type II variation procedure for Humira, a centrally authorised medicine containing adalimumab, to update the RMP to review the specified safety concerns and bring it in line with revision 2 of GVP Module V on 'Risk management systems'. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Humira (adalimumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 14.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed with the proposed revision of the list of safety concerns. In addition, the PRAC agreed with the discontinuation of the requirement for educational material for healthcare professionals (HCPs) as an additional risk minimisation measure as it is considered that the risks are well known in clinical practice. With regard to the patient reminder card, the PRAC supported to update it in relation to live vaccinations given to in utero adalimumab exposed infants to more precisely address this. Annex II should be updated accordingly.

5.2.2. Dexamethasone - NEOFORDEX (CAP) - EMEA/H/C/004071/II/0008

Applicant: Laboratoires CTRS

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 4.0) in order to propose the 'removal of the score line for subdivision of the 40mg tablet and consequent deletion of the 20mg posology' as a category 3 activity. In addition, the MAH updated the other category 3 activity: 'development of a 20mg oral dosage form'. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

Background

Dexamethasone is a synthetic glucocorticoid indicated for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

The PRAC is evaluating a type II variation procedure for Neofordex, a centrally authorised medicine containing dexamethasone, to update the RMP in order to remove a category 3 activity on the 'removal of the score line for subdivision of the 40 mg tablet and consequent deletion of the 20 mg posology' as well as to update the category 3 activity on 'development of a 20 mg oral dosage form'. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Neofordex (dexamethasone) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 4.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the requirement for the MAH to submit a marketing authorisation application (MAA) for a 20 mg oral dosage form within 12 months of the European Commission (EC) decision grating a marketing authorisation (MA) to Neofordex (dexamethasone) 40 mg tablets has not been fully met. In addition, the PRAC concluded that the MAH's rationale to delete the category 3 activity of 'removal of the score line for sub-division of the 40 mg tablet, and consequent deletion of the 20 mg posology' is not acceptable at present. Finally, the MAH is requested to re-evaluate the list of safety specifications in line with revision 2 of GVP module V on 'Risk management systems'.

5.2.3. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0084

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 18.0) in order to remove the educational programme for prescribing healthcare professionals as an additional risk minimisation measure based on the outcome of the PSUSA procedure (PSUSA/00001560/201704) concluded at the December 2017 PRAC meeting

Background

Golimumab is a human monoclonal antibody that binds specifically to tumour necrosis factor (TNF) and inhibits the biological function of TNF. It is indicated, as Simponi, for the treatment of rheumatoid arthritis (RA), of juvenile idiopathic arthritis including polyarticular juvenile idiopathic arthritis (pJIA) and psoriatic arthritis (PsA), of axial spondyloarthritis including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-Axial SpA), and for the treatment of ulcerative colitis (UC) under certain conditions.

The PRAC is evaluating a type II variation procedure for Simponi, a centrally authorised medicine containing golimumab, to update the RMP in order to remove the educational programme for prescribing healthcare professionals as an additional risk minimisation measure (aRMM) based on the conclusions of the latest PSUSA procedure. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Simponi (golimumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 18.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed with the discontinuation of the requirement for educational material for healthcare professionals (HCPs) as an aRMM as it is considered that the risks are well known in clinical practice. In addition, the PRAC supported that the patient card remains as it was considered important that patients are well aware of the risks of the medicinal product and seek medical advice and care for as needed. As a consequence, Annex II should be updated accordingly.

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

See also Annex I 15.3.

5.3.1. Arsenic trioxide - TRISENOX (CAP) - EMEA/H/C/000388/X/0068

Applicant: Teva B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to add a new strength of 2 mg/mL (concentrate for solution for solution for infusion) in vials. The RMP (version 2.0) is updated accordingly

Background

Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukaemia (PML) cells *in vitro* and also causes damage or degradation of the fusion protein pro-myelocytic leukaemia/retinoic acid receptor-alpha (PML/RAR alpha). It is indicated, as Trisenox, for induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) in combination with all-*trans*-retinoic acid (ATRA) or relapsed/refractory APL, characterised by the presence of the t(15;17) translocation and/or the presence of the PML/retinoic acid receptor (RAR) alpha gene.

The CHMP is evaluating an extension of application to add a new strength. The RMP is proposed to be updated to include in particular 'medication errors related to possible confusion between the two presentations' as a new important potential risk and to bring in line the RMP with revision 2 of the guidance on the format of RMP in the EU (template). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- The RMP for Trisenox (arsenic trioxide) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 2.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered the potential risk of confusion between the authorised strength (1mg/mL) and the proposed new one (2mg/mL) that could potentially lead to medication errors despite the difference in presentation between an ampoule and vial. The PRAC advised to add 'medication errors related to possible confusion between the two presentations' as a new important potential risk. In addition, the MAH is requested to provide a thorough discussion on the magnitude of the risk and consequences of the dosing errors (underdosing and overdosing) as well as a proposal for further routine risk minimisation measures to highlight the differences between the two presentations. Moreover, the MAH should discuss possible activities to evaluate the effectiveness of the risk minimisation measures, and justify the need for a PASS, if this is considered necessary. Finally, the PRAC did not support the current proposal from the MAH to distribute a direct healthcare professional communication (DHPC) in light of the currently available data. Therefore, the MAH should be requested to further elaborate on its proposal.

5.3.2. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/X/0044/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations; 2) extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The package leaflet, labelling and the RMP (version 13.0) are updated accordingly. In addition, Annex II is updated to be brought in line with the latest QRD template (version 10)

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or adult patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The CHMP is evaluating a grouping of applications consisting of an extension of application to introduce a new strength to the currently approved presentations and of an extension of indication to add a new indication for the treatment of paediatric patients with relapsing multiple sclerosis (RMS). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see PRAC minutes March 2018 and PRAC minutes July 2018.

Summary of advice

- The RMP for Gilenya (fingolimod) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 13.2 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- In terms of safety specifications, the PRAC confirmed that 'convulsion' should be listed as an important identified risk and 'long term use in paediatric patients, including impact on growth and development (including cognitive development)' as missing information. The MAH should also closely monitor all important identified/potential risks and missing information for the paediatric population specifically, and provide a cumulative review in the next PSUR (data lock point (DLP): 28/02/2019). In relation to 'psychiatric disorders in paediatric patients', the PRAC supported the MAH's proposal to closely monitor this topic. While at present information in the product information appears sufficient, the PRAC agreed that further evidence is required before considering inclusion of this matter into the RMP as an important safety concern.
- With regard to the pharmacovigilance plan, the PRAC agreed with the MAH's proposal to recruit additional patients in the paediatric sub-population of the current 5-year long term extension of study D2311[28], instead of putting in place a new safety study. Nevertheless, the MAH should ensure that safety assessments are included in study D2311 and modify the selection criteria in order to include patients, such as those with highly active RRMS for the age groups ≤12 years, ≤40 kg or Tanner stage <2 (pre-pubertal) group. In addition, the PRAC requested the MAH to provide interim safety data for this specific subpopulation as planned in Q2 2020 and submit subsequent reports on a yearly basis.
- As for the risk minimisation measures, the physician information pack should include the summary of product characteristics (SmPC) and an update of the educational materials/physician checklist for both adults and paediatric patients together with the patient/parent/caregiver reminder card. Finally, a recommendation for physicians to consider re-assessing annually the benefit versus risks in each patient should also be included, with particular regards to paediatric patients.

5.3.3. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0020

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as

[28] A two year double-blind, randomized, multicentre, active controlled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a intramuscular (i.m) once weekly in paediatric patients with multiple sclerosis with five-year fingolimod extension phase

monotherapy for the treatment of adult patients with BRCA-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. Those patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 16) are updated accordingly

Background

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

The CHMP is evaluating an extension of the therapeutic indication for Lynparza, a centrally authorised product containing olaparib, to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with BRCA-1/2-mutated human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer who have previously been treated with chemotherapy. 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 June 2018.

Summary of advice

- The RMP for Lynparza (olaparib) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC reiterated that the important identified risk of anaemia should be removed from the list of safety concerns in line with revision 2 of GVP module V on 'risk management systems'. In addition, the wording of the important potential risk on medication errors as proposed by the MAH should be reworded as 'medication errors associated with dual availability of capsules and tablets'. The PRAC also agreed that missing information should be updated with 'long-term exposure to/potential toxicity of olaparib'.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Axitinib - INLYTA (CAP) - PSUSA/00010022/201801

Applicant: Pfizer Limited

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

Background

Axitinib is a selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. It is indicated, as Inlyta, for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Inlyta (axitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the risk of aneurysm rupture in order to ensure careful consideration before initiating axitinib therapy in patients with pre-existing aneurysms and to add 'aneurysm rupture' as an example under the undesirable effect on bleeding. Therefore, the current terms of the marketing authorisation(s) should be varied[29].
- The MAH should submit to EMA an updated RMP in line with revision 2 of GVP module V on 'risk management systems' and PRAC comments within the next upcoming regulatory procedure affecting the RMP or at the latest within six months.
- In the next PSUR, the MAH should provide detailed reviews of cases of fractures, cases of interstitial lung disease (ILD) and cases of cholecystitis.

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. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201801

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Dasabuvir is a non-nucleoside inhibitor of the hepatitis C virus (HCV) ribonucleic acid (RNA)-dependent RNA polymerase encoded by the non-structural protein 5B (NS5B) gene indicated, as Exviera, in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Exviera (dasabuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'diarrhoea' as an undesirable effect with a frequency 'very common', 'vomiting' with a frequency 'common' and 'dehydration' with a frequency 'uncommon', when identified with Exviera (dasabuvir) in combination with ombitasvir/paritaprevir/ritonavir and ribavirin. Therefore, the current terms of the marketing authorisation(s) should be varied[30].
- The MAH should submit to EMA, within 60 days, a detailed review of the signal of hepatic failure in patients with Child-Pugh A (compensated).
- In the next PSUR, the MAH should closely monitor cases of thrombocytopenia and provide a detailed analysis of cases of depression.

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. Dexamethasone[31] - OZURDEX (CAP) - PSUSA/00000985/201801 (with RMP)

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a corticosteroid indicated, as Ozurdex, for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy, as well as for the treatment of adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). It is also indicated for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ozurdex (dexamethasone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be amended to update the undesirable effect 'complication of device insertion' to 'complication of device insertion resulting in ocular tissue injury'. Therefore, the current terms of the marketing authorisation(s) should be varied[32].

[30] 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
[31] Centrally authorised product(s) only, indicated in the treatment of uveitis and macular oedema
[32] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should provide a review on 'vision impairment associated with implant misplacement or migration'. In addition, the MAH should assess whether a further warning for 'device insertion in patients with vitrectomy with an implant misplacement or migration' is warranted in the product information.

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

6.1.4. Fingolimod - GILENYA (CAP) - PSUSA/00001393/201802

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or adult patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Gilenya (fingolimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include safety information on the effect of fingolimod on human papillomavirus (HPV) infections and to add 'myalgia' and 'arthralgia' as undesirable effects with a frequency 'common'. In addition, the product information section on undesirable effects is further amended to include updated information regarding lymphomas and cases of cutaneous T-cell lymphoma (mycosis fungoides). Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- The MAH should submit to EMA, within 60 days, a detailed review of the potential benefit of Gilenya (fingolimod) use in pregnant women and women of child-bearing potential (WCBP) not using effective contraception and whether it can outweigh the identified reproductive toxicity and risk of teratogenicity. The MAH should discuss what would be the implications of a contra-indication in the treatment of highly active RRMS in pregnant women and in WCBP who do not use effective contraception. The discussion

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

should include a general overview, including the half-life and duration of exposure to fingolimod, as well as the potential for disease rebound following discontinuation. In addition, the review should include updated information on reproductive toxicity. Finally, in light of the use of Gilenya (fingolimod) in pregnant women despite the current existing recommendations, the MAH should propose further risk minimisation measures (RMM) to reduce the risk of exposure during pregnancy.

- In the next PSUR, the MAH should provide a review of cases of weight loss. With regard to auto-immune haemolytic anaemia, see also 4.1.1.

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.

6.1.5. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201801

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

Background

Ingenol mebutate has shown in *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate is indicated as Picato, for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Picato, a centrally authorised medicine containing ingenol mebutate and issued a recommendation on its marketing authorisation(s). For further background, see PRAC minutes July 2018.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Picato (ingenol mebutate) 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 a proper meta-analysis of the skin malignancy data from ingenol disoxate studies LP0084-1193[34] and LP0084-1196[35], giving full details of the statistical methods used. The available data for ingenol disoxate and ingenol mebutate should be evaluated to determine whether there is evidence of an interaction by site of application and whether these data are supportive of a dose-response relationship. In relation to study LP0105-1032[36], the MAH should provide the details of the numbers censored and discuss the impact this may have had on the hazard ratios. In addition, the MAH should discuss all options for further studies to

[34] A phase 3 trial on efficacy and safety of ingenol disoxate (LEO 43204) in field treatment of actinic keratosis on face or chest including 12-month follow-up
[35] A phase 3 trial on efficacy and safety of ingenol disoxate (LEO 43204) in field treatment of actinic keratosis on balding scalp including 12-month follow-up
[36] A phase 3, international, randomised, parallel-group, double-blind, vehicle-controlled trial with a duration of 12 months to compare the short term efficacy of ingenol mebutate gel 0.027% with vehicle gel in AK when applied topically once daily for 3 consecutive days as field treatment

obtain further long-term safety data for Picato (ingenol mebutate), including both clinical trial and observational study designs. Any study should include at least 18 months of follow-up of skin malignancy, a total number of treated actinic keratosis lesions at least comparable to that of the disoxate studies, and comparison with either vehicle or a range of other actinic keratosis treatments. The MAH should also discuss whether any further non-clinical studies are ongoing or planned to better elucidate the mechanism of action of ingenol esters. Moreover, the important potential risk of 'actinic keratosis to squamous cell carcinoma (SCC) progression' should be updated to 'new skin tumours in treatment area'. Study LP0041-63[37] should continue to be an additional pharmacovigilance activity for this safety concern, along with the proposed new study. The RMP should be updated accordingly.

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. Meningococcal group-B vaccine (rDNA[38], component, adsorbed) - BEXSERO (CAP) - PSUSA/00010043/201801 (with RMP)

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Meningococcal group-B vaccine (rDNA, component, adsorbed) is indicated, as Bexsero, for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bexsero, a centrally authorised vaccine containing meningococcal group-B vaccine (rDNA, component, adsorbed) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Bexsero (meningococcal group-B vaccine (rDNA, component, adsorbed)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'meningeal irritation' with a frequency 'not known' and to add a short description to the term stating that symptoms such as photophobia and neck stiffness have been sporadically reported and that these events have been of mild and transient nature. Therefore, the current terms of the marketing authorisation(s) should be varied[39].

[37] A phase 4 trial comparing the cumulative incidence of squamous cell carcinoma (SCC) after treatment with ingenol mebutate and imiquimod for multiple actinic keratoses on face and scalp: a multicentre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial
[38] Recombinant deoxyribonucleic acid
[39] 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

- In the next PSUR, the MAH should provide a cumulative review of cases of stroke evaluating demography, time to onset (TTO), availability of medical history, clinical presentation including magnetic resonance imaging (MRI) results when available.

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

6.1.7. Nalmefene - SELINCRO (CAP) - PSUSA/00010120/201802

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Nalmefene is an opioid system modulator with a distinct μ, δ, and κ receptor profile indicated, as Selincro, for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms and who do not require immediate detoxification.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Selincro (nalmefene) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'priapism', 'angioedema', 'urticaria', 'pruritus', 'rash' and 'erythema' with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[40].

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

6.1.8. Nitisinone - ORFADIN (CAP) - PSUSA/00002169/201802

Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Nitisinone is a competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase indicated, as Orfadin, for the treatment of adult and paediatric patients with confirmed diagnosis of

[40] 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

hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Orfadin (nitisinone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on 'monitoring of plasma tyrosine levels' to add a recommendation with regards to regular examination of the eyes after treatment initiation. Therefore, the current terms of the marketing authorisation(s) should be varied[41].
- The MAH should submit to EMA, within 60 days, the complete data set from Sobi.NTBC-006[42] clinical trial related to the interactions with the investigated isoforms of CYP450[43] and the organic anion transporters and propose to update the product information as warranted.
- The MAH should submit to EMA an exhaustive evaluation on 'incidence of liver cancer' within the final report of study Sobi. NTBC-005 (OPAL)[44], expected in April 2020.

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. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201801

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

Background

Ritonavir is a CYP3A[45] inhibitor, ombitasvir a hepatitis C virus (HCV) non-structural 5A (NS5A) inhibitor and paritaprevir an HCV non-structural protein 3/4A (NS3/4A) protease inhibitor. In combination, ombitasvir/paritaprevir/ritonavir is indicated together with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

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

Summary of recommendation(s) and conclusions

[41] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[42] An open-label, non-randomized, 2-arm, 2-period fixed sequence phase 1 study to evaluate the potential inhibition of nitisinone on cytochrome P450 2C9, 2D6, and 2E1 and the organic anion transporters OAT1 and OAT3 in healthy volunteers
[43] Cytochrome P450
[44] A non-interventional, non-comparative, multicentre PASS to evaluate long-term safety of orfadin treatment in HT-1 patients in standard care
[45] Cytochrome P450, family 3, subfamily A

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Viekirax (ombitasvir/paritaprevir/ritonavir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'diarrhoea' as an undesirable effect with a frequency 'very common', 'vomiting' with a frequency 'common' and 'dehydration' with a frequency 'uncommon', when identified with Viekirax (ombitasvir/paritaprevir/ritonavir) in combination with dasabuvir and ribavirin. Therefore, the current terms of the marketing authorisation(s) should be varied[46].
- The MAH should submit to EMA, within 60 days, a detailed review of the signal of hepatic failure in patients with Child-Pugh A (compensated).
- In the next PSUR, the MAH should closely monitor cases of thrombocytopenia and provide a detailed analysis of cases of depression.

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

6.1.10. Prasugrel - EFIENT (CAP) - PSUSA/00002499/201802 (with RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of adenosine diphosphate (ADP) receptors on platelets. It is indicated, as Efient, co-administered with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Efient (prasugrel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on interaction between prasugrel and morphine when co-administered as it reduces prasugrel efficacy. Indeed, a delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including prasugrel and its active metabolite, has been observed in patients with acute

[46] 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

coronary syndrome treated with morphine. Therefore, the current terms of the marketing authorisation(s) should be varied[47].

- The PRAC considered that the risk of interaction between morphine and prasugrel could be relevant for other medicinal products within the same class of $P2Y_{12}$ inhibitors. As a result, MAHs of centrally authorised products of the class of $P2Y_{12}$ inhibitors should consider updating their product information accordingly in a relevant regulatory procedure, should their product information not reflect this risk yet.

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

6.1.11. Ranolazine - RANEXA (CAP) - PSUSA/00002611/201801 (with RMP)

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Ranolazine reduces intracellular ionic imbalances during ischaemia. It is indicated, as Ranexa, in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ranexa (ranolazine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning to specify that the observed QT prolongation is dose dependent. In addition, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to remove the additional risk minimisation measures as the relevant safety information of the educational materials is contained in the product information and the management of risks has been integrated into routine clinical practice. Therefore, the current terms of the marketing authorisation(s) should be varied[48].

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.

[47] Update of SmPC sections 4.4 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
[48] Update of SmPC section 4.8 and Annex-D. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.12. Vismodegib - ERIVEDGE (CAP) - PSUSA/00010140/201801

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Vismodegib is an orally available small-molecule inhibitor of the Hedgehog pathway indicated, as Erivedge, for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and for the treatment of adult patients with locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Erivedge (vismodegib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'drug induced liver injury' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[49].
- In the next PSUR, the MAH should provide clarification on the surveys measuring the effectiveness of the pregnancy prevention programme (PPP), including a discussion on whether the evaluation of the effectiveness of the PPP can be improved. This should include consideration of addition and/or revision of measurement process indicators (knowledge) and outcome indicators (recommendations given by physicians) in order to measure the effectiveness of the PPP in line with the latest recommendations in revision 2 of GVP module XVI on 'risk minimisation measures: selection of tools and effectiveness indicators'.

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

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

See also Annex I 16.2.

6.2.1. Alitretinoin - PANRETIN (CAP); NAP - PSUSA/00000090/201801

Applicants: Eisai Ltd (Panretin), various

PRAC Rapporteur: Julie Williams

[49] 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

Scope: Evaluation of a PSUSA procedure

Background

Alitretinoin is a naturally occurring endogenous hormone, related to vitamin A, which binds to and activates all known intracellular retinoid receptor subtypes. It is indicated, as a gel, for the topical treatment of cutaneous lesions in patients with acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) when lesions are not ulcerated or lymphoedematous, when the treatment of visceral KS is not required, when lesions are not responding to systemic antiretroviral therapy, and when radiotherapy or chemotherapy are not appropriate. It is also indicated orally for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of alitretinoin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'hair texture changes' as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisations should be varied[50].

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

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

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

See also Annex I 16.3.

6.3.1. 5-fluorouracil[51] (NAP) - PSUSA/00000007/201712

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

[50] 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
[51] Intravenous (I.V) application only

5-fluorouracil is a pyrimidine analogue indicated intravenously for the treatment of gastrointestinal neoplasm malignant (including gastric, colon, pancreatic carcinoma, oesophageal carcinoma, advanced colorectal, rectal carcinoma), head and neck cancer (including squamous cell carcinoma of head and neck), epidermoid carcinoma, advanced and/or metastatic, breast carcinoma/adenocarcinoma, malignant respiratory tract neoplasm (including bronchial carcinoma, lung cancer), liver tumour, cervix carcinoma, bladder carcinoma, ovarian carcinoma/adenocarcinoma, uterine carcinoma and prostatic carcinoma.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 5-fluorouracil for intravenous (IV) application and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of 5-fluorouracil for intravenous application-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity and a warning regarding the risk of severe toxicity in patients with DPD deficiency. Warnings are also added in relation to cardiotoxicity and encephalopathy. In addition, 'febrile neutropenia' should be added as an undesirable effect with a frequency 'common', 'infections' with a frequency 'very common', cardiac arrest with a frequency 'very rare', pericarditis with a frequency not known, hyperammonaemic encephalopathy with a frequency 'not known' and clarifications that leukoencephalopathy is not dose- or DPD deficiency-dependent are added. Moreover, the product information is updated to delete any reference to the fact that no antidote exists. Therefore, the current terms of the marketing authorisation(s) should be varied[52].
- In the next PSUR, the MAHs should provide a detailed review of the literature on therapeutic drug monitoring (TDM) of 5-fluorouracil including in particular the publications by *Wilhelm et al. 2016*[53], *Beumer et al. 2018*[54] and *Lee et al. 2016*[55]*.* The review should include a feasibility assessment of implementing TDM in clinical practice. The MAH(s) should consider updating the product information as warranted. Moreover, the MAH(s) should monitor further developments and provide a detailed discussion on genotyping of DPYD (e.g. new variants), on other methods to determine DPD activity (e.g. phenotyping) and on genetic variants of other enzymes associated with an increased toxicity of fluoropyrimidines. The MAH(s) should provide a discussion on the need to update the product information. The MAH(s) should also discuss newly generated data from on-going studies and latest developments in dosing guidelines on genotype-guided dosing of 5-fluorouracil and assess the need to update the product information accordingly.

[52] Update of SmPC sections 4.3, 4.4, 4.8, 4.9 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

[53] Wilhelm M, Mueller L, Miller MC, Link K, Holdenrieder S, Bertsch T, Kunzmann V, Stoetzer OJ, Suttmann I, Braess J, Birkmann J, Roessler M, Moritz B, Kraff S, Salamone SJ, Jaehde U. Prospective, multicentre study of 5-fluorouracil therapeutic drug monitoring in metastatic colorectal cancer treated in routine clinical practice. Clin Colorectal Cancer. 2016 Dec;15(4):381-388

[54] Beumer JH, Chu E, Allegra C, Tanigawara Y, Milano G, Diasio R, Won Kim T, Mathijssen RH, Zhang L, Arnold D, Muneoka K, Boku N, Joerger M. Therapeutic drug monitoring in oncology: International association of therapeutic drug monitoring and clinical toxicology (IATDMCT) recommendations for 5-fluorouracil therapy. Clin Pharmacol Ther. 2018 Jun 20

[55] Lee JJ, Beumer JH, Chu E. Therapeutic drug monitoring of 5-fluorouracil. Cancer Chemother Pharmacol. 2016 Sep;78(3):447-64

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

6.3.2. 5-fluorouracil[56] (NAP) - PSUSA/00010000/201712

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

5-fluorouracil is a pyrimidine analogue indicated topically for the treatment of superficial pre-malignant and malignant skin lesions; keratoses including senile, actinic and arsenical forms; keratoacanthoma; Bowen's disease; erythroplasia of Queyrat; superficial basal-cell carcinoma and acuminated condyloma.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing 5-fluorouracil for topical application and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of 5-fluorouracil for topical application-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a cumulative review of all cases of application site discharge and application site/skin haemorrhage including a comprehensible causality assessment and propose to update the product information as warranted.

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

6.3.3. Aldesleukin (NAP) - PSUSA/00000076/201712

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Aldesleukin is an immunostimulant belonging to the class of cytokines and immunomodulators. Aldesleukin is indicated for the treatment of metastatic renal cell carcinoma.

[56] Topical application only

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of aldesleukin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'influenza like illness', 'hyponatraemia' and 'hypophosphatemia' as undesirable effects with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[57].

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

6.3.4. Allopurinol (NAP) - PSUSA/00000095/201712

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Allopurinol is a xanthine-oxidase inhibitor indicated for the treatment of gout, primary and secondary hyperuricemia and resulting diseases (ureate nephropathy, urea acid and calcium oxalate stones), for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy), or in enzyme disorders that lead to overproduction of urate.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of allopurinol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'angioedema' and 'anaphylactic reaction' as undesirable effects with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[58].
- In the next PSUR, the MAHs should provide a detailed review of the literature on prevalence of HLA[59]-B*5801 in patients taking allopurinol, in particular the publication

[57] 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
[58] 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

by *Yu et al.*[60] suggesting a higher prevalence for the HLA-B*58:01 genotype in specific European subpopulations. MAHs should propose to update the product information as warranted. In addition, the MAHs should provide a review of cases of meningitis/encephalitis and of the literature, and propose to update the product information as warranted.

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

6.3.5. Amantadine (NAP) - PSUSA/00000126/201801

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Amantadine is a synthetic tricyclic amine indicated for the treatment of Parkinson's disease (PD) under certain conditions as well as for the prophylaxis against infections with influenza type A virus.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amantadine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on impulse-control disorders (ICD) and on visual problems. ICD should be also added as an undesirable effect with a frequency 'not known' and eye disorders with a frequency 'uncommon' (i.e. blurred vision) and 'rare' (i.e. corneal lesion). Therefore, the current terms of the marketing authorisation(s) should be varied[61].
- In the next PSUR, the MAHs should provide a cumulative review of cases of suicidal ideation and suicide attempt/completed suicide.

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.

[59] Human leukocyte antigen
[60] Yu K. H., Yu C. Y., Fang Y. F. (2017). Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: an updated systematic review and meta-analysis. Int JRheum Dis
[61] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.6. Amitriptyline, perphenazine (NAP) - PSUSA/00000170/201801

Applicant(s): various

PRAC Lead: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Amitriptyline is a tricyclic antidepressant and perphenazine a piperazine derivative. In combination, amitriptyline/perphenazine is indicated for the treatment of depression associated with anxiety.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amitriptyline/perphenazine-containing medicinal products 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 cases of hypersensitivity, drug-induced liver injury (DILI), insomnia, somnolence, tardive dyskinesia, overdose, use in pregnancy and lactation as well as use in paediatrics and adolescents.

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

6.3.7. Amitriptyline (NAP); amitriptyline, amitriptylinoxide (NAP); amitriptylinoxide (NAP) - PSUSA/00010374/201801

Applicant(s): various

PRAC Lead: Agni Kapou

Scope: Evaluation of a PSUSA procedure

Background

Amitriptyline, amitriptyline oxide and amitriptyline N-oxide are tricyclic antidepressants. Amitriptyline, amitriptyline/amitriptylinoxide and amitriptylinoxide are indicated for the treatment of major depressive disorder in adults, for the treatment of neuropathic pain in adults, for the prophylactic treatment of chronic tension type headache (CTTH) in adults as well as the prophylactic treatment of migraine in adults. They are also indicated for the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of amitriptyline-, amitriptyline/amitriptylinoxide- and amitriptylinoxide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add an interaction with valproic acid as amitriptyline plasma concentration can be increased by sodium valproate and valpromide. In addition, the undesirable effect of 'hallucination (in schizophrenic patients)' should be adjusted to 'hallucination' with no reference to schizophrenic patients. Moreover, 'hyponatraemia' should be added to the section on overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[62].
- In the next PSUR, the MAH should provide a discussion on the following safety concerns: drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity, cardiac arrest, pregnancy, lactation and congenital malformations, interaction with warfarin, dementia, post-partum haemorrhage, pre-eclampsia, metabolic acidosis due to overdose, rhabdomyolysis, facial paresis, hypoesthesia oral, lack of therapeutic efficacy (mainly linked to suicidality, overdose, interactions and drug abuse), purpura, interaction between anticholinergic drugs (amitriptyline) and acetylcholinesterase inhibitors (AChEI).
- The PRAC considered that the risks of hallucinations, hyponatraemia and interaction with valproic acid are also relevant for the following fixed dose combinations: amitriptyline/perphenazine, amitriptyline/chlordiazepoxide and amitriptyline/medazepam. Further consideration is to be given at the level of the CMDh.

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

6.3.8. Bendroflumethiazide (NAP); bendroflumethiazide, potassium chloride (NAP) - PSUSA/00010583/201801

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

Background

Bendroflumethiazide is a thiazide diuretic. Bendroflumethiazide alone or in combination with potassium chloride are indicated for the treatment of hypertension, oedema related to heart insufficiency, oedema of another genesis, prophylaxis against recurrent renal calcium stones and diabetes insipidus.

[62] Update of SmPC sections 4.5, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing bendroflumethiazide and bendroflumethiazide/potassium chloride and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bendroflumethiazide and bendroflumethiazide/potassium chloride-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on significant hypercalcaemia being the possible sign of hyperparathyroidism and on possible interference of thiazides with test of parathyroid function. In addition, 'hypercalcaemia' is added as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[63].
- In the next PSUR, the MAH(s) should provide a detailed analysis for the safety concerns of fluid and electrolyte disturbances, hypersensitivity, aggravation of diabetes mellitus, renal impairment, and exacerbation of systemic lupus erythematosus as well as foetal and neonatal toxicity when used in pregnancy.

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

6.3.9. Cisplatin (NAP) - PSUSA/00000778/201712

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Cisplatin is a platinum-based heavy metal coordination complex with antineoplastic activity through inhibition of DNA[64] synthesis. It is indicated for the treatment of testicular tumours (including extragonadal germ-cell tumours), ovarian carcinoma, lung cancer (both small and non-small cell carcinoma) and head and neck cancer and cervical carcinoma in combination with other chemotherapeutics or with radiotherapy under certain conditions. It is also locally authorised in certain EU member states for the treatment of thyroid cancer and lymphoma, prostate cancer and tumours in stage 3 and stage 4 metastasised in the abdominal cavity or in organs.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of cisplatin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'venous thromboembolism' as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[65].
- In the next PSUR, the MAH should maintain 'hypersensitivity and anaphylactic reaction' as an important identified risk. In addition, the MAH should provide cumulative reviews on infusion time, hydration and supplementation strategies.
- Based on the reviews of all information on infusion time, hydration and supplementation strategies, the MAH(s) should submit relevant variations to the National Competent Authorities (NCA) as applicable. Further consideration is to be given at the level of the CMDh.

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

6.3.10. Dapoxetine (NAP) - PSUSA/00000928/201712

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Dapoxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of premature ejaculation (PE) in adult men aged 18 to 64 years.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of dapoxetine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add grapefruit juice (potent CYP3A4[66] inhibitor) as interacting with dapoxetine. Grapefruit juice should be avoided within 24 hours prior to taking dapoxetine. Therefore, the current terms of the marketing authorisation(s) should be varied[67].

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.

[65] 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
[66] Cytochrome P450 3A4
[67] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.11. Gemcitabine (NAP) - PSUSA/00001519/201801

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Gemcitabine is a nucleoside analogue of deoxcytidine and a pyrimidine antimetabolite. It is indicated for the treatment of non-small-cell lung carcinoma (NSCLC), pancreatic cancer, urothelial cancer (bladder, renal pelvis, ureter, and urethra), breast cancer, ovarian cancer, cervical cancer and biliary tract cancer.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gemcitabine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'thrombotic microangiopathy' as an undesirable effect with a frequency 'very rare', 'infection' with a frequency 'common', as well as 'sepsis' and 'pseudocellulitis' with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[68].

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

6.3.12. Levonorgestrel (NAP) - PSUSA/00001856/201712

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Levonorgestrel is a second generation progestin (synthetic progesterone) indicated in oral contraception, heavy menstrual bleeding (hypermenorrhea, idiopathic menorrhagia) and emergency contraception. It is also indicated in some EU Member states for the protection from endometrial hyperplasia during oestrogen replacement therapy.

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

[68] 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 benefit-risk balance of levonorgestrel-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the package leaflet for levonorgestrel tablets indicated for emergency contraception should be updated to include a black box to emphasise the appropriate schedule of drug administration of levonorgestrel in this indication. Therefore, the current terms of the marketing authorisation(s) should be varied[69].
- The current terms of the marketing authorisation(s) for the other pharmaceutical forms and indications covered in this PSUSA should be maintained.
- In the next PSUR, the MAH(s) for levonorgestrel-containing intra-uterine devices (IUDs) should present cases of 'weight increase/gain' with a positive/negative de-/and rechallenge in order to check for a non-biased causality as 'weight gain' is already listed in some product information. The MAH(s) should also provide a review of cases of 'dizziness' and propose an update of the product information as warranted. In addition, the MAH(s) should also present a detailed review of 'primary fallopian tube carcinoma' including a causality assessment and a thorough literature review. Furthermore, the MAH(s) should provide reviews of cases of 'erythema nodosum', 'drug induced liver injury' and 'pseudotumor cerebri/idiopathic intracranial hypertension'.
- In the next PSUR, the MAH(s) of levonorgestrel-only oral contraceptive should provide a detailed reviews of cases reported with concurrent use of lamotrigine and on 'potential for decreased contraceptive efficacy in overweight women' including pharmacokinetic (PK) and pharmacodynamic (PD) data, proposing to update the product information as warranted.
- In the next PSUR, the MAH(s) for levonorgestrel-containing tablets for emergency contraception should provide a detailed review of 'muscle spasm' and propose an update of the product information as warranted. The MAH(s) should also present detailed review of cases of 'anaphylaxis' and of 'delayed menstrual period > 60 days and amenorrhea'.
- In the next PSUR, all MAH(s) should provide an assessment of the effectiveness of routine risk minimisation measures addressing the important risks.
- With regard to levonorgestrel-containing IUDs, the PRAC considered that the effectiveness and necessity of the currently available educational materials should be re-evaluated. In addition, the PRAC considered that the 'risk of expulsion of levonorgestrel-containing IUDs in obese women' should be further assessed in depth. Further consideration is to be given at the level of the CMDh.

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

[69] Update of the package leaflet section 3. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6.3.13. Valproic acid (NAP); sodium valproate (NAP); valproate pivoxil (NAP); valproate semisodium (NAP); valpriomide (NAP); valproate bismuth (NAP); calcium valproate (NAP); valproate magnesium (NAP) - PSUSA/00003090/201801

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Valproic acid and related substances (sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate and valproate magnesium) are indicated for the treatment of epilepsy and for the treatment of manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in some EU Member States in prophylaxis of migraine attacks.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate and valproate magnesium and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of valproic acid-, sodium valproate-, valproate pivoxil-, valproate semisodium-, valpriomide-, valproate bismuth-, calcium valproate- and valproate magnesium-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'diplopia' with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied[70].
- In the next PSUR, the MAH should provide a detailed review of the article by *Durá-Travé T et al. 2018* [71] and propose to update the product information regarding vitamin D supplementation in valproate users as warranted. In addition, the MAH(s) should present a review of cases of 'impaired growth children' and discuss the need to update the product information accordingly.

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

[70] 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

[71] Durá-Travé T, Gallinas-Victoriano F, Malumbres-Chacón M, Moreno-Gónzalez P, Yoldi-Petri M. Vitamin D deficiency in children with epilepsy taking valproate and levetiracetam as monotherapy. Epilepsy Research. Volume 139, January 2018, Pages 80-84 (https://doi.org/10.1016/j.eplepsyres.2017.11.013)

6.4.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/LEG 010.1

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to LEG 010 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in February 2018

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated, as Stayveer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[72] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a detailed description of the educational materials with the controlled distribution systems implemented at national levels in order to assess the effectiveness of each measure in place to minimise any risk, and hence measure whether the risk minimisation measures (RMMs) in place are still relevant or not (for background, see PRAC minutes July 2017 and PRAC minutes February 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice / conclusion(s)

- The PRAC considered that the MAH should submit to EMA, within 60 days, a variation[73] to update Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to delete from the additional risk minimisation measures (RMMs) the requirement to distribute a prescriber kit to healthcare professionals (HCPs) as these have been implemented for a long period of time and it is considered that HCPs are well trained and aware of the management of the risks of bosentan. In addition, some RMMs have become part of standard clinical practice and are no longer necessary in view of the knowledge gained over the years. Nevertheless, the PRAC advised to maintain the patient alert card as it is a significant tool to ensure that patient are aware of the risk of hepatotoxicity and the recommendation for adequate use of contraceptive method.

6.4.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/LEG 086.1

Applicant: Actelion Registration Limited

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's responses LEG 086 [overview of the educational materials with the controlled distribution systems implemented at national levels, together with a discussion on the

[72] World Health Organization
[73] Annex II. The RMP is to be updated accordingly

effectiveness of each measure in place to minimise any risk (including educational material and controlled distribution system), as requested in the conclusions of PSUSA/00000425/201611 adopted in July 2017] as per the request for supplementary information (RSI) adopted in February 2018

Background

Bosentan is a dual endothelin receptor antagonist (ERA) indicated, as Tracleer, for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[74] functional class III. It is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a detailed description of the educational materials with the controlled distribution systems implemented at national levels in order to assess the effectiveness of each measure in place to minimise any risk, and hence measure whether the risk minimisation measures (RMMs) in place are still relevant or not (for background, see PRAC minutes July 2017 and PRAC minutes February 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice / conclusion(s)

- The PRAC considered that the MAH should submit to EMA, within 60 days, a variation[75] to update Annex II on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' in order to delete from the additional risk minimisation measures (RMMs) the requirement to distribute a prescriber kit to healthcare professionals (HCPs) as these have been implemented for a long period of time and it is considered that HCPs are well trained and aware of the management of the risks of bosentan. In addition, some RMMs have become part of standard clinical practice and are no longer necessary in view of the knowledge gained over the years. Nevertheless, the PRAC advised to maintain the patient alert card as it is a significant tool to ensure that patient are aware of the risk of hepatotoxicity and the recommendation for adequate use of contraceptive method.

6.4.3. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/LEG 036.1

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to LEG 036 [review of cases of tumefactive lesions reported in the literature and in post marketing setting, as requested in the conclusions of PSUSA/00001393/201702 adopted by PRAC at its October 2017 meeting] as per the request for supplementary information (RSI) adopted in March 2018

Background

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated, as Gilenya, as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for adult patients with highly active disease despite a full and adequate course of treatment with

[74] World Health Organization
[75] Annex II. The RMP is to be updated accordingly

at least one disease modifying therapy or adult patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit a further review of cases of tumefactive lesions reported in the literature and in post marketing setting (for background, see PRAC minutes October 2017 (25-29 September) and PRAC minutes March 2018). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC considered that the MAH should submit to EMA, within 60 days, a variation[76] to update the warning section of the product information to reflect that rare cases of tumefactive lesions associated with RRMS were reported in the post-marketing setting. In case of severe relapses, MRI should be performed to exclude tumefactive lesions. Discontinuation of Gilenya (fingolimod) should be considered by the physicians on a case-by-case basis taking into account individual benefits and risks.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[77]

None

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[78]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[79]

7.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0015

Applicant: Janssen Pharmaceutical Companies of Johnson & Johnson

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to PSR/S/0016 [results of a drug utilisation study (DUS) of domperidone in Europe using databases to investigate the effectiveness of risk minimisation measures and to describe the prescribing patterns before and after the changes to the domperidone label in routine clinical practice in selected European countries, as required in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013] as per the request for supplementary information (RSI) adopted in March 2018

Background

[76] Update of SmPC section 4.4. The package leaflet is to be updated accordingly
[77] In accordance with Article 107n of Directive 2001/83/EC
[78] 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
[79] In accordance with Article 107p-q of Directive 2001/83/EC

Domperidone is a D_2-receptor antagonist indicated for the relief of the symptoms of nausea and vomiting. In line with the conclusions reached in 2014 of the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1365) conducted by the PRAC for domperidone-containing medicines, MAHs were required as a condition to the marketing authorisations (Annex IV) to conduct a drug utilisation study (DUS) in several Member States to assess the effectiveness of the agreed risk minimisation measures and to monitor off-label use. The study protocol was to be submitted within 3 months after the European Commission decision. In October 2016, the PRAC endorsed the PASS (drug utilisation study (DUS)) protocol version 2 (dated 20 July 2016) submitted by the MAH Janssen Research and Development on behalf of a group of MAHs (the Domperidone Collaboration Study Group). For further background, see PRAC minutes March 2014, PRAC minutes April 2015, PRAC minutes September 2015, PRAC minutes January 2016, PRAC minutes June 2016 and PRAC minutes October 2016.

The final study report was submitted to EMA by the MAH Janssen Research and Development on behalf of the Consortium (Domperidone Collaboration Study Group) on 18 December 2017. For further background, see PRAC minutes March 2018. The PRAC discussed the final study results in addition to the MAH's answers to the request for supplementary information (RSI).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'a drug utilisation study of domperidone in Europe using databases', as well as the MAH's responses to the RSI, the PRAC considered that a further RSI was necessary before a recommendation could be made on the benefit-risk balance of medicinal products containing domperidone concerned by the PASS final report.
- The MAH is requested to provide a direct healthcare professional communication (DHPC) along with a communication plan reminding the restricted indication to nausea and vomiting as well as the contraindications regarding the use of CYP3A4[80] inhibitors and in case of hepatic impairment in addition to the cardiac severe side effects, contraindications linked to cardiac records and the use of cardiotropic treatments and treatment duration.
- The MAH is also requested to provide the DHPC and communication plan adopted in the context of the referral procedure under Article 31 of Directive 2001/83/EC for domperidone-containing products (EMEA/H/A-31/1365).
- Furthermore, the PRAC considered that the MAH should propose measures to assess the effectiveness of risks minimisation measures including the DHPC.
- The MAH should submit responses to the request for supplementary information within 30 days to EMA. A 30 days-assessment timetable will be applied.

7.3.2. Magnesium sulphate heptahydrate, sodium sulphate anhydrous, potassium sulphate (NAP) - EMEA/H/N/PSR/S/0016

Applicant: Ipsen Pharma (Eziclen, Izinova)

PRAC Rapporteur: Adrien Inoubli

[80] Cytochrome P 450 3A4

Scope: MAH's response to PSR/S/0016 [results for a multicentre, European, observational, drug utilisation study (DUS) of Eziclen/Izinova (BLI800) (magnesium sulfate heptahydrate/sodium sulfate anhydrous/potassium sulfate) as a bowel cleansing preparation to document the misuse of BLI800, defined as non-compliance in terms of sufficient liquid intake, during the post approval period in the real life setting; and to describe the safety profile of BLI800 in routine clinical practice, overall and in cases of misuse defined as non-compliance in terms of sufficient liquid intake, and identify any immediate/acute adverse events associated with the use of BLI800 in special populations (i.e. the elderly and patients at risk for electrolyte shifts)] as per the request for supplementary information (RSI) adopted in May 2018

Background

In January 2013, Eziclen/Izinova, an oral solution composed of sulfate salts of sodium, potassium and magnesium, was authorised in adults, via the decentralised procedure (DCP) (FR/H/511/01/DC), for bowel cleansing prior to any procedure requiring a clean bowel (e.g. bowel visualisation including endoscopy and radiology or surgical procedures). The post-marketing commitments that accompanied the approval included the requirement for the MAH to conduct a drug utilisation study (DUS) to assess drug utilisation in the real life setting in a representative sample of the European target population. The PASS protocol version 4 was endorsed by PRAC in March 2015 (see PRAC minutes March 2015).

The final study report dated 2 February 2018 was submitted to EMA by the MAH Ipsen Pharma SAS on 6 March 2018. For further background, see the PRAC minutes May 2018. The PRAC discussed the final study results in addition to the MAH's answers to the RSI.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'a multicentre, European, observational, DUS of BLI800 as a bowel cleansing preparation', the PRAC considered that the benefit-risk balance of Eziclen/Izinova (magnesium sulphate heptahydrate, sodium sulphate anhydrous, potassium sulphate) remains unchanged. As a consequence, the PRAC recommended that the terms of the marketing authorisation(s) for Eziclen/Izinova (magnesium sulphate heptahydrate, sodium sulphate anhydrous, potassium sulphate) should be varied to remove the PASS as an obligation 'to perform a post authorisation safety study (PASS) to assess drug utilisation in real life setting in a representative sample of the European target population' from the 'conditions or restrictions with regard to the safe and effective use of the medicinal product'.

7.3.3. Piperaquine tetraphosphate, artenimol – EURARTESIM (CAP) - EMEA/H/C/PSR/S/0018

Applicant: Alfasigma S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Results of a safety registry study in the EU assessing the association between the QTc prolongation induced by Eurartesim (piperaquine tetraphosphate/artenimol) and various factors, co-morbidities and concomitant medications, as well as at monitoring patterns of drug utilisation

Background

Piperaquine is a bisquinoline and dihydroartemisinin (DHA) is a semi-synthetic derivative of artemisinin. Eurartesim is a combination of these substances, which is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more.

Eurartesim, a centrally authorised medicine containing piperaquine tetraphosphate/dihydroartemisinin, was authorised in 2011. As a condition to the marketing authorisation (Annex II-D), the MAH was required to set up a PASS[81] to further substantiate the cardiac safety of Eurartesim use in patients with signs and symptoms of uncomplicated malaria, including the effect of Eurartesim administration on QTc intervals. The MAH shall provide the results of an epidemiological study addressing this issue, according to a CHMP agreed protocol.

The final study report was submitted to EMA by MAH Alfasigma S.p.A on 19 June 2018. The PRAC discussed the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report version 1.0 of the non-interventional PASS entitled 'safety registry for Eurartesim: an observational, non-comparative, non-interventional, longitudinal, multi-centre safety registry for malaria patients treated with Eurartesim', the PRAC considered that a request for supplementary information (RSI) was necessary before a recommendation could be made on the benefit-risk balance of Eurartesim (piperaquine tetraphosphate/artenimol) concerned by the PASS final report.
- The MAH is requested to consider reclassifying the event of abnormal liver function based on the study result, discuss the inclusion of abnormal renal test in the product information based on the cases reported in the PASS, explore the available data supporting a dose-response relationship for the adverse events of special interest and further explore the data suggesting that both risk of QT prolongation and liver abnormalities (increase in transaminases levels) are influenced by smoking status.
- The MAH should submit responses to the request for supplementary information within 60 days to EMA. A 60 days-assessment timetable will be applied.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[82]

See also Annex I 17.4.

7.4.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/II/0038

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report for study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess the effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

Action: For adoption of PRAC Assessment Report

[81] EUPAS6942. Safety registry for Eurartesim: an observational, non-comparative, non-interventional, longitudinal, multi-centre safety registry for malaria patients treated with Eurartesim

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

Background

Thymanax is a centrally authorised medicine containing agomelatine, a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist. Thymanax (agomelatine) is indicated in adult patients for the treatment of major depressive episodes.

As stated in the RMP of Thymanax (agomelatine), the MAH conducted a non-imposed non-interventional PASS (CLE-20098-096, DUS) to assess the effectiveness of risk minimisation measures (RMMs) of Thymanax/Valdoxan (agomelatine). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes June 2018.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- In addition, the MAH is requested to submit to EMA within 60 days a critical and comprehensive review of the PASS study results. Based on this review, and on post-marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity, the MAH should discuss if additional RMMs should be continued and, if so, should be improved. Moreover, the MAH should investigate and discuss whether liver function testing prior to and during treatment with agomelatine is regarded as standard of care in the EU Member States.

7.4.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0039

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: Submission of the final report for study CLE-20098-096 (listed as a category 3 study in the RMP): a non-interventional PASS, drug utilisation study (DUS) to assess effectiveness of risk-minimisation measures of Thymanax/Valdoxan (agomelatine)

Background

Valdoxan is a centrally authorised medicine containing agomelatine, a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist. Valdoxan (agomelatine) is indicated in adult patients for the treatment of major depressive episodes.

As stated in the RMP of Valdoxan (agomelatine), the MAH conducted a non-imposed non-interventional PASS (CLE-20098-096, DUS) to assess the effectiveness of risk-minimisation measures (RMMs) of Thymanax/Valdoxan (agomelatine). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see PRAC minutes June 2018.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.
- In addition, the MAH is requested to submit to EMA within 60 days a critical and comprehensive review of the PASS study results. Based on this review, and on post-

marketing observational studies and available pharmacovigilance data in relation to hepatotoxicity, the MAH should discuss if additional RMMs should be continued and, if so, should be improved. Moreover, the MAH should investigate and discuss whether liver function testing prior to and during treatment with agomelatine is regarded as standard of care in the EU Member States.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None

7.8. Ongoing Scientific Advice

None

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

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

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

8.1. Annual reassessments of the marketing authorisation

None

8.2. Conditional renewals of the marketing authorisation

None

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Ustekinumab – STELARA (CAP) - EMEA/H/C/000958/II/0066

Applicant: Janssen-Cilag International

PRAC Rapporteur: Patrick Batty

Scope: Consultation on a type II variation to update section 4.8 of the SmPC to add 'allergic alveolitis' and 'eosinophilic pneumonia' as adverse drug reactions with a frequency 'rare'. The package leaflet is updated accordingly

Background

Stelara is a centrally authorised medicine containing ustekinumab, a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23. Stelara (ustekinumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults under certain conditions, the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older under certain conditions, the treatment of active psoriatic arthritis in adult patients, alone or in combination with methotrexate (MTX) under certain conditions and the treatment of adult patients with moderately to severely active Crohn's disease under certain conditions.

A type II variation proposing to update the product information of Stelara (ustekinumab) to add allergic alveolitis and eosinophilic pneumonia as undesirable effects[83] is under evaluation at the CHMP further to the review of two successive cumulative reviews of cases related to interstitial lung disease (PSUSA/00003085/201612) as well as a cumulative review of cases reporting eosinophilic lung inflammation and related events. For further background, see PRAC minutes July 2017. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC discussed the MAH's proposal to update the product information with allergic alveolitis and eosinophilic pneumonia reported during the post-marketing use of Stelara (ustekinumab) and proposed to include warnings and precautions for use on the matter[84] given that healthcare professionals might benefit from having more detailed information including

[83] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[84] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

recommendations for discontinuation and treatment rather than only the inclusion of those reported events as undesirable effects. In addition, the PRAC supported the update of the product information to include allergic alveolitis and eosinophilic pneumonia as undesirable effects[85] with a frequency 'rare'.

- Given that only a very small number of cases suggestive of fibrotic or remodelling events were reported, and those were limited by confounding factors, the PRAC considered that there may not be sufficient evidence at this point to include further updates in the product information. However, due to the severity of the cases, the PRAC proposed to request a cumulative review of pulmonary fibrotic or remodelling events in the next PSUR (data lock point (DLP): 31/12/2018), and to request the company to comment on whether an additional update of the product information is warranted.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Celecoxib (NAP) - SE/H/xxxx/WS/186, SE/H/xxxx/WS/204, SE/H/xxxx/WS/210

Applicant(s): Pfizer AB (Celebra, Celecoxib Pfizer, Solexa)

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on variation procedures assessing the final results of a post-approval study: 'a prospective randomized evaluation of celecoxib integrated safety *vs.* ibuprofen or naproxen (PRECISION)' and proposed changes in the product information, on request of Sweden

Background

Celecoxib is a cyclooxygenase2 (COX-2) selective nonsteroidal anti-inflammatory drug (NSAID) (a coxib) used for the treatment of pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation and juvenile rheumatoid arthritis, under certain conditions.

[85] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Due to emerging safety data, various reviews, also in the context of referrals procedures (CHMP/323166/05; EMEA/H/A-5.3/800; EMEA/H/A-5(3)/1319; EMEA/H/A-31/1344), have been conducted for coxibs and NSAIDs regarding cardiovascular safety, leading to various updates of the product information.

In the context of the evaluation of two type II variation procedures (SE/H/xxxx/WS/186 and SE/H/xxxx/WS/210) for which the MAH for celecoxib proposes an update of the product information[86] based on the PRECISION[87] post-approval study, Sweden requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC agreed with Sweden's conclusion that due to insufficient data, the MAH proposals to remove the contraindication for celecoxib in patients with established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease and replace it with a warning statement concerning use in these patient groups, were not acceptable.
- Moreover, the PRAC also supported the inclusion of the PRECISION study results in the product information[88] and supported a refined wording proposal for this matter.

11.1.2. Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034

Applicant(s): Bayer BV (Qlaira)

PRAC Lead: Menno van der Elst

Scope: PRAC follow-up consultation on a national variation procedure to assess the final results of an imposed cohort study INAS-SCORE: 'an international active surveillance study, safety of contraceptives: role of estrogens' conducted in the US and Europe and the proposed amendments to the product information on the risk of venous thromboembolism (VTE), on request of the Netherlands

Qlaira, a combined oral contraceptive (COC) containing estradiol valerate (EV) as an oestrogen and dienogest (DNG) as a progesterone component is used for contraception and the treatment of heavy menstrual bleeding in women without organ pathology who desire oral contraception.

Further to the submission by the MAH of the final study report II of INAS-SCORE, performed to assess the risk of venous thromboembolism (VTE) associated with Qlaira (DNG/EV) and the subsequent MAH's proposal to update the product information (PI)[89], the Netherlands requested in February 2018 PRAC advice on its assessment of the final results of the INAS-SCORE study and the MAH's proposals for updating the product information to include the findings of this study. It was considered that further clarifications on the study results were needed before any conclusions could be drawn regarding the risk of VTE associated with Qlaira (DNG/EV). As a result, the PRAC supported addressing a list of questions (LoQ) to the MAH in relation to the study results as well as further on a request for supplementary information (RSI). For further background information, see PRAC minutes February 2018 and PRAC minutes July 2018. The MAH replied to the reference member state (RMS), the

[86] Proposed update of SmPC sections 4.3, 4.4 and 5.1. The PIL is proposed to be updated accordingly
[87] Prospective randomized evaluation of celecoxib integrated safety vs. ibuprofen or naproxen
[88] Update of SmPC section 5.1
[89] Update of SmPC section 4.4. The package leaflet is updated accordingly

Netherlands, to the second request for supplementary information, and the responses were assessed by the RMS. The RMS concluded that the MAH presented sufficient clarification and concluded that the responses given do not indicate that the validity of the results of the INAS study should be questioned. Therefore, the Netherlands considered that the PI changes as proposed by the MAH could be acceptable, provided the further changes recommended by the RMS are implemented. The Netherlands requested PRAC advice on its assessment, conclusions and proposals for PI update.

Summary of advice

- The PRAC reviewed the assessment, conclusions and recommendations by the RMS, and highlighted some concerns on the lack of discriminatory study power to show a difference in the VTE risk associated with Qlaira in comparison to specific COCs, including levonorgestrel (LNG)-containing COCs, as the study was designed to exclude a two-fold increase in comparison to all other COCs. It was also noted as a limitation that the study was not able to discriminate between the known higher VTE risk of CHCs containing drospirenone, gestodene or desogestrel in comparison to CHCs containing LNG despite exposure to these CHCs being higher than for Qlaira implying sufficient accrual of data within the study for conducting respective analysis.
- Nevertheless, the PRAC supported the RMS' views that the current information in the product information stating that the VTE risk associated with Qlaira is unknown was no longer valid. Taking into consideration the above, the PRAC favoured a cautious approach with regards to updating the PI on the VTE risk to convey information in a manner which reflects the actual data and its limitations, and as such, provided a proposal to amend the PI[90] accordingly.
- Noting the limitations of the INAS-SCORE study, the PRAC advised that it is important that the PI wording informing about the comparative risk of VTE among different CHCs highlights that the use of CHCs with a known low VTE risk such as CHCs containing levonorgestrel, norethisterone or norgestimate is preferably considered before using other products including Qlaira.
- Besides, the PRAC highlighted that the overall evidence on the CHC risk of Qlaira is currently limited to the INAS-SCORE single study and pointed out that it would be highly desirable to obtain further study data from any other data sources to support the findings of the INAS-SCORE study and to further quantify the VTE risk associated with Qlaira.

11.1.3. General anaesthetics and sedatives: Desflurane (NAP); enflurane (NAP); etomidate (NAP); esketamine (NAP); halothane (NAP); isoflurane (NAP); ketamine (NAP); midazolam (NAP); propofol (NAP); sevoflurane (NAP); thiopental (NAP)

Applicants: various

PRAC Lead: Ghania Chamouni

Scope: PRAC follow-up consultation on the scientific relevance to update the product information for general anaesthetics and sedative medicines regarding the risk of developmental disorders when used in children and pregnant women, in light of available

[90] Proposal to update section 4.4 of the SmPC and the package leaflet accordingly

safety data from preclinical and clinical studies, FDA action taken in April 2017, national variations submitted for isoflurane-, sevoflurane- and propofol-containing medicines, and PRAC advice adopted in January 2018 including the Safety Working Party (SWP) responses, on request of France

Background

General anaesthetics are a structurally diverse group of compounds whose mechanisms encompass multiple biological targets involved in the control of neuronal pathways. General anaesthetics, however, typically elicit several key reversible effects: analgesia, amnesia, unconsciousness, immobility, and reduced autonomic responsiveness to noxious stimuli. Sedatives are central nervous depressants and interact with brain activity causing its deceleration. They induce sedation by reducing irritability or excitement.

In the context of the evaluation of type II variation procedures in view of amending the product information of isoflurane-, sevoflurane- and propofol-containing products, France sought in January 2018 PRAC advice on its assessment of the scientific relevance to update the product information for general anaesthetics and sedative medicines regarding the risk of developmental disorders when used in children and pregnant women, given the available safety data from preclinical and clinical studies, the FDA action taken in April 2017, and national variations submitted for isoflurane, sevoflurane and propofol. At the time, on the basis of the provided assessment, the PRAC did not support the addition of the proposed warning in the product information[91]. As the clinical significance of the non-clinical data remains unclear and no firm recommendations can be given, the usefulness of this information for prescribers would be limited. The inclusion of relevant information in the preclinical safety data[92] section was considered to be in principle sufficient. Nevertheless, the PRAC advised that the exact wording for this section of the product information should be further considered after consultation with the CHMP Safety Working Party (SWP). Subsequently, France liaised with the CMDh and SWP in order to further review the robustness of the data before any decision on possible regulatory action could be proposed (see PRAC minutes January 2018). Based on the SWP advice, France recommends the update of the product information[93] of all anaesthetics as data is considered insufficient to conclude that the risks are different between the products.

Summary of advice

- Based on the review of the available information as well as the SWP advice, the PRAC supported the update of product information[94].
- Of note, no update of the sedatives (midazolam and dexmedetomidine) product information (PI) is proposed given that no convincing data are available, and there are not sufficient grounds for extrapolating the class effect of anaesthetics to sedatives.

Post meeting note: A list of substances concerned by the PI update was further defined at the CMDh meeting September 2018 as follow: desflurane, enflurane, etomidate, esketamine, halothane, isoflurane, ketamine, propofol, sevoflurane, thiopental, methohexital; (all pharmaceutical forms).

[91] Update of SmPC sections 4.4 and 4.6
[92] Update of SmPC section 5.3
[93] Update of SmPC sections 4.6 and 5.3
[94] Update of SmPC section 5.3 with the corresponding cross-reference in section 4.6

11.2. Other requests

11.2.1. Thiocolchicoside (NAP) - EMEA/H/N/PSA/J/0010

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: PRAC follow-up consultation on the evaluation of a progress report for a non-interventional imposed PASS: a drug utilisation study assessing the effectiveness of risk minimisation measures (routine and additional) and further characterising the prescribing patterns for thiocolchicoside-containing medicinal products for systemic use, following the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC finalised in 2014, on request of Italy

Background

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with muscle relaxant pharmacological activity indicated as an adjuvant for the treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16-years onwards.

In line with the conclusions of a referral procedure under Article 31 of Directive 2001/83/EC conducted in 2014 for thiocolchicoside-containing medicines (EMEA/H/A-1361), MAHs were required as a condition to the marketing authorisations (Annex IV) to provide within the risk management plan submission a protocol to evaluate the effectiveness of the risk minimisation activities. The final study report had to be submitted by November 2017 (within 18 months after the EC decision). On 21 December 2017 the Consortium of the MAHs submitted the first PASS interim report for thiocolchicoside to the Italian Medicines Agency (AIFA). For background information, see PRAC minutes February 2013, PRAC minutes January 2017, and PRAC minutes June 2017. In the context of the national evaluation of the study progress report, Italy requested PRAC advice on its assessment, see PRAC minutes March 2018 and the PRAC supported the Italian request for supplementary information for the Consortium of MAHs to provide AIFA with the requested clarifications on the PASS interim data. Italy requested PRAC advice on its assessment of the requested clarifications, and conclusions.

Summary of advice

- Based on the review of the available information and in light of the results of the interim report as well as of the Consortium's responses to the list of questions, the PRAC supported the proposal from Italy for a re-distribution of the additional risk minimisations measures (aRMMs) to re-iterate the key messages implemented within the 2014 referral procedure. In addition, the PRAC supported the proposed risk minimisation strategy, including the healthcare professional (HCP) guide, the patient card and a direct healthcare professional communication (DHPC), as well as the proposed revisions to the DHPC and communication plan.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC Vice-Chairperson - election

Following the election of Sabine Straus as the new Chairperson in July 2018 with a mandate starting on 3 September 2018 (see PRAC minutes July 2018), the PRAC proceeded with the election of the vice-Chairperson as per the principles discussed in April 2018 (see PRAC minutes April 2018). The election of a new vice-Chairperson took place on 5 September 2018. The EMA Secretariat reminded the PRAC members of the Rule of Procedure (EMA/PRAC/567515/2012 Rev.1) pertaining to the election of the vice-Chairperson as well as the election process. Candidate(s) addressed the PRAC. The election took place in the presence of 35 PRAC members out of which 34 were eligible to vote[95]. Martin Huber, PRAC member for Germany, was elected as PRAC vice-Chair. His mandate will start on 1 October 2018 for a term of three years, which may be prolonged once. The newly elected vice-Chair thanked the Committee.

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. Scientific Advice Working Party (SAWP) – call for expression of interest for a joint SAWP-PRAC alternate

Following the last meeting dated June 2018 of Hervé Le Louet as a PRAC independent expert appointed by the European Commission (EC) and the subsequent nomination of six new independent expert starting their mandates in July 2018, the EMA Secretariat launched a call for expression of interest to replace him as the joint PRAC-SAWP alternate to support Brigitte Keller-Stanislawski in her role of joint PRAC-SAWP member. Candidates were invited to send their nominations by 29 August 2018. Further discussion will take place in due course.

12.4. Cooperation within the EU regulatory network

12.4.1. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group – Call for expression of interest for a PRAC representative

Following the departure of Marie-Louise (Marieke) de Bruin from PRAC as an independent expert in June 2018, a call for expressions of interest for a PRAC representative to the ENCePP Steering Group (ENCePP SG) was launched to replace her in this quality. The PRAC was informed that Daniel Morales was appointed as the new PRAC representative to the ENCePP SG.

[95] Icelandic and Norwegian members do not vote for the PRAC Chairperson election as per the PRAC Rules of Procedure. At the current meeting, there was no PRAC representative from Iceland

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, Maia Uusküla

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

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 September 2018, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of September 2018, the updated EURD list was adopted by the CHMP and CMDh at their September 2018 meetings and published on the EMA website on 26/09/2018, see:

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

Following the appointment of Sabine Straus as the new PRAC Chair as of 3 September 2018, a call for expression of interest was launched for members to become co-chair of the SMART Processes working group. As an outcome, Menno van der Elst was appointed for this role. The PRAC congratulated him and thanked Sabine Straus for her dedication and leadership during the past six years as co-chair of the SMART Processes working group.

The PRAC was also updated on the pilot on signal detection by MAHs in EudraVigilance. Following the request from the EMA to the European Commission (EC) to extend the pilot beyond February 2019 in view of Brexit, the EC agreed with it. The PRAC was informed that EMA plans to finalise a report on the pilot by September 2019. Based on this report, a decision will be made by end of 2019 on the next steps to further implement the EudraVigilance monitoring by MAHs.

Finally, the PRAC was informed that a further call for expression of interest for Lead Member States (LMS) within the signal management worksharing will be launched towards the end of 2018.

12.12. Adverse drug reactions reporting and additional monitoring

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 03/10/2018 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

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management plan (RMP) – Results of the monitoring exercise of the quality of submissions under RMP revision 2

At the organisational matters teleconference held on 20 September 2018, and in line with the PRAC work plan 2018, the EMA Secretariat presented to PRAC a status update of the project on monitoring RMP submissions consisting of a qualitative analysis of such submissions in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template). Overall, the findings are positive. A further revision of the guidance on the format of RMP in the EU (template) is planned for discussion at PRAC in October 2018. This revision will not impact on the structure and will provide further additional guidance.

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Communication on safety referrals at the time of CMDh position and European Commission (EC) decision –Review process

At the organisational matters teleconference held on 20 September 2018, the EMA Secretariat presented to PRAC a proposal to refine the communication contents for safety referral procedures at the time of PRAC recommendation, CMDh position and EC decision as applicable. This aims at streamlining the review procedure and maintaining consistency of message to reassure readers that the scientific content remains unchanged for CMDh position endorsing PRAC recommendations. In the case the CMDh adopts a different position, a new communication will be published. Some standard text communication was presented to PRAC. The committee supported the amendments. This was also agreed at the level of the CMDh.

12.18.2. PRAC communication – call for expression of interest to review communication strategy and materials

As a result of the election of Sabine Straus as the new Chairperson of the Committee with a mandate that started on 3 September 2018, the EMA Secretariat launched a 'call for expression of interest for a communication expert' to replace her in this role to work alongside Amelia Cupelli with the support of the EMA medical and health information service.

Post-meeting note: At the October 2018 PRAC meeting, Julia Pallos and Sophia Trantza were nominated as communication experts.

12.18.3. Public participation in pharmacovigilance

None

12.18.4. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Brexit preparedness - EMA measures and business continuity plan

The EMA Secretariat presented to PRAC an outline of phase 3 of the Agency's measures and business continuity plan in the context of the Brexit preparedness. Details can be found on

the following EMA webpage entitled 'Brexit preparedness: EMA to further temporarily scale back and suspend activities' dated 1 August 2018. Further updates will be scheduled in due course.

12.20.2. EMA funded post-authorisation efficacy and safety research - Generating evidence to support regulatory decision-making

As a follow-up to the July 2018 discussion (see PRAC minutes July 2018), the EMA Secretariat presented the initiative of EMA funded post-authorisation efficacy and safety research to support regulatory decision-making and a proposal for PRAC involvement in this process. The presentation included information on the new framework contract, an overview of the tendering process and a proposal for Committee scientific input in the tender deliverables, including options for handling potential conflicts of interest of Committee members employed by contracted research institutions. The PRAC was also updated on the status of the draft technical specifications for two impact studies on valproate and retinoids that were endorsed by the Committee. In addition, as a follow up to the July 2018 discussion, PRAC delegates were requested to further prioritise shortlisted topics for impact research through EMA's new framework contact. Answers should be sent by 12 September 2018. Further discussion will be scheduled in due course.

12.20.3. Good Pharmacovigilance Practices (GVP) – revisions during 2018 - 2019 - revision cycle

The PRAC was provided with its regular overview of the GVP module status made on a quarterly basis, last update was made in July 2018 (see PRAC minutes July 2018). This update shows the status of ongoing or planned work on new or revised GVP modules together with their scope and proposed timelines for 2019. This takes into consideration the current EMA measures and business continuity plan in the context of the Brexit preparedness. In view of the latter, PRAC agreed to suspend the quarterly updates until September 2019.

See also 12.20.1.

12.20.4. Telematics - Concept paper on strategy 2020-2025

The EMA Secretariat presented to PRAC a concept paper to establish the telematics strategy for 2020-2025 in order to ensure that information management and technology appropriately represents the EU network's business needs. The concept paper outlines the direction that the development of telematics strategy 2020-2025 should take and assures, early on, that there is adequate top-down strategic direction for business changes that the EU network will have to make over the period of time to inform information management changes. The document will serve as a foundation for drafting the new telematics strategy 2020-2025 including the bottom up consultation with all major partner and stakeholder groups, in particular EMA scientific committees. PRAC delegates were invited to provide comments by 15 October 2018. Comments received will be considered in the drafting of the telematics strategy 2025 by the network information-technology (IT) directors' executive committee.

13. Any other business

Next meeting on: 01-04 October 2018

14. Annex I – Signals assessment and prioritisation[96]

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[97].

14.1.1. Apixaban – ELIQUIS (CAP)

Applicant(s): Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pancreatitis

EPITT 19265 – New signal

Lead Member State(s): NL

14.1.2. Gabapentin (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of dysphagia

EPITT 19296 – New signal

Lead Member State(s): DE

14.1.3. Voriconazole – VFEND (CAP)

Applicant(s): Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19276 – New signal

Lead Member State(s): NL

[96] [96] 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

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

14.2. New signals detected from other sources

14.2.1. Denosumab – PROLIA (CAP)

Applicant(s): Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of alopecia

EPITT 18332 – New signal

Lead Member State(s): SE

14.2.2. Nivolumab – OPDIVO (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of scleroderma

EPITT 19282 – New signal

Lead Member State(s): DE

14.2.3. Pazopanib – VOTRIENT (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Signal of rhabdomyolysis

EPITT 19281 – New signal

Lead Member State(s): DK

14.2.4. Pemetrexed – ALIMTA (CAP); NAP

Applicant(s): Eli Lilly Nederland B.V. (Alimta), various

PRAC Rapporteur: Ghania Chamouni

Scope: Signal of syncope

EPITT 19289 – New signal

Lead Member State(s): FR

14.2.5. Sunitinib – SUTENT (CAP)

Applicant(s): Pfizer Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Signal of aortic dissection

EPITT 19283 – New signal

Lead Member State(s): IT

14.2.6. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of psoriasis

EPITT 19273 – New signal

Lead Member State(s): DE

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. Pegfilgrastim - EMEA/H/C/004915

Scope: Treatment of neutropenia

15.1.2. Trastuzumab - EMEA/H/C/004916

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

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

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

15.2.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1402/0038; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1402/0038

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 7.0) in order to reflect changes in categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.2. Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1403/0023; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1403/0023

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4.0) in order to reflect changes in categorisation of safety concerns and missing information in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.3. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0015

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 2.0) in order to update the requirements for a planned study (listed as a category 3 in the RMP): a multicentre, observational, non-interventional European study of patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.4. Capecitabine - XELODA (CAP) - EMEA/H/C/000316/II/0077

Applicant: Roche Registration GmbH

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 9.1) in line with the product information changes recently approved within variation II/0074 concluded in March 2018. These include an update of the post-authorisation exposure, an update of the important identified risk 'dihydropyrimidine dehydrogenase deficiency (DPD)' and updates related to section 4.4 of the EU SmPC for DPD. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.5. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/II/0030, Orphan

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 2.10) in order to revise the risk re-categorisation justifications and lay language wording, as well as to add clarifications to the described additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures and set up date of EU network of laboratories, as requested by PRAC following the assessment of the annual renewal procedure completed in February 2018

15.2.6. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/II/0038

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 20.0) in order to streamline and improve the educational programme and communication to prescribing physicians as requested in variation II/0035 concluded in June 2018

15.2.7. Peginterferon alfa-2a - PEGASYS (CAP) - EMEA/H/C/000395/II/0101

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 9.0) in order to remove NV25361 study (listed as a category 3 study in the RMP): a phase 3b, randomized, open-label study of pegylated interferon alfa-2a in combination with lamivudine or entecavir compared with untreated control group in children with hepatitis B envelope antigen (HBeAg)-positive chronic hepatitis B (CHB) in the immune-tolerant phase. In addition, YV25718 study: a phase 3b parallel group, open label study of pegylated interferon alfa-2a monotherapy (PEG-IFN, Ro 25-8310) compared to untreated control in children with HBeAg positive chronic hepatitis B (study to establish the efficacy and safety of PEG-IFN monotherapy in children from 3 to less than 18 years of age with chronic hepatitis B) long term follow up milestone is amended from Q3 2020 to Q4 2021. In addition, the MAH took the opportunity to reflect changes in categorisation of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' including updates in the epidemiology section

15.2.8. Sitagliptin - JANUVIA (CAP) - EMEA/H/C/000722/WS1357/0063; RISTABEN (CAP) - EMEA/H/C/001234/WS1357/0055; TESAVEL (CAP) - EMEA/H/C/000910/WS1357/0063; XELEVIA (CAP) - EMEA/H/C/000762/WS1357/0067; sitagliptin, metformin hydrochloride - EFFICIB (CAP) - EMEA/H/C/000896/WS1357/0089; JANUMET (CAP) - EMEA/H/C/000861/WS1357/0089; RISTFOR (CAP) - EMEA/H/C/001235/WS1357/0076; VELMETIA (CAP) - EMEA/H/C/000862/WS1357/0092

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Updated RMP (version 9.1) in order to remove 'theoretic carcinogenic potential' currently classified as missing information from the list of safety concerns in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

15.2.9. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0045, Orphan

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of the RMP (version 8) in order to include the safety information from the final clinical study report (CSR) of study TED-C14-006 (listed as a category 3 study): a 24-week double-blind, safety, efficacy, and pharmacodynamic study investigating two doses of teduglutide in paediatric subjects aged 1 year through 17 years with short bowel syndrome

who are dependent on parenteral support following the ongoing assessment by CHMP of variation II/0043

15.2.10. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0190

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Update of the RMP (version 22.1) in line with revision 2 of GVP module V on 'Risk management systems' to propose the removal of additional risk minimisation activities on renal safety associated with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) affected adults

15.2.11. Zoledronic acid - ZOLEDRONIC ACID MYLAN (CAP) - EMEA/H/C/002482/WS1370/0015

Applicant: Mylan S.A.S

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 7.0) to implement the latest RMP template and to include 'and other anatomical sites' in addition to 'osteonecrosis of the jaw' as an important identified risk, to be aligned with the conclusions of the PSUSA procedure for zoledronic acid (PSUSA/00003149/201608) concluded by PRAC/CHMP in April 2017

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. Adalimumab - CYLTEZO (CAP) - EMEA/H/C/004319/II/0004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 1297.3 (listed as a category 3 study in the RMP): an interventional trial to generate long-term safety, efficacy, and immunogenicity data for the administration of Cyltezo (adalimumab, biosimilar) in patients with moderate to severe rheumatoid arthritis (RA). The RMP (version 2.0) is updated accordingly

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0007/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) extension of indication to include in combination with bevacizumab, paclitaxel and carboplatin the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), based on the interim results of study GO29436: a phase 3, open-label, randomized study of atezolizumab in combination with carboplatin+paclitaxel with or without bevacizumab compared with

carboplatin+paclitaxel+bevacizumab in chemotherapy-naïve patients with stage IV NSCLC (IMpower 150). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated; 2) update of section 4.8 of the SmPC in order to update the monotherapy safety data and reflect the largest pooled monotherapy population available (including data from study IMvigor211: a phase 3, open-label, multicentre, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy, and study PCD4989g: a phase 1, open-label, dose-escalation study of the safety and pharmacokinetics of atezolizumab administered intravenously as a single agent to patients with locally advanced or metastatic solid tumours or hematologic malignancies). The package leaflet and the RMP (version 4.0) are updated accordingly. In addition, the MAH took the opportunity to introduce small corrections and formatting changes throughout the SmPC

15.3.3. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/II/0002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension of indication to include all adult patients with moderate or severe chronic obstructive pulmonary disease (COPD). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to add the results of two phase 3 studies, namely: 1) study Triple 7 (CCD-05993AA1-07): a multinational, multicentre, randomised, open-label, active-controlled, 26-week, 2-arm, parallel group study to evaluate the non-inferiority of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pressurised metered dose inhaler (pMDI) (CHF 5993) *vs* fixed combination of fluticasone furoate plus vilanterol administered via dry powder inhaler (DPI) (Relvar) plus tiotropium bromide (Spiriva) for the treatment of patients with COPD; 2) study Triple 8 (CCD-05993AA1-08): a 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro) via DPI in patients with COPD (TRIBUTE). The package leaflet and the RMP (version 5.0) are updated accordingly

15.3.4. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0005

Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the treatment of hepatocellular carcinoma in adults following prior systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the RMP (version 4.2) are updated accordingly

15.3.5. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/X/0025

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form (film-coated tablets). The RMP (version 12) is updated accordingly

15.3.6. Choriogonadotropin alfa - OVITRELLE (CAP) - EMEA/H/C/000320/II/0073/G

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to indicate that thromboembolism can also occur without the presence of ovarian hyperstimulation syndrome (OHSS). The package leaflet and the RMP (version 6.0) are updated accordingly; 2) update of the RMP to extend the important potential risk of 'misuse' to 'weight loss and anabolic growth promoting effect'. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet, to make editorial changes in the product information and in Annex A (list of authorised presentations). The MAH also took the opportunity to make some minor revisions in the RMP.

15.3.7. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0059

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia for the treatment of paediatric patients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 16.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the product information

15.3.8. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0005/G

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report for study ELX-PH-08 (listed as a category 3 study in the RMP). This is an in vitro evaluation study aimed to investigate the effects on treating primary cultures of cryopreserved human hepatocytes with eluxadoline on the expression of cytochrome P450 (CYP) enzymes; 2) submission of the final report for study 3030-102-002 (listed as a category 3 study in the RMP). This is a randomised, open label study aimed to evaluate the effect of eluxadoline as a potential time dependent inhibitor of CYP3A4[98] with the substrate midazolam. The RMP (version 2.0) is updated to refine the important identified risk of 'sphincter of Oddi (SO) spasm' to 'SO spasm (sphincter of Oddi dysfunction, SOD)' and to include pancreatitis as an important identified risk as agreed in the conclusions of PSUSA/00010528/201703 finalised at PRAC/CHMP in October 2017

[98] Cytochrome P 450 3A4

15.3.9. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0039/G

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.7, 4.8 and 5.2 of the SmPC in order to amend the warning on possible association with seizure, to amend the effects on driving or operating machines, to amend the identified adverse reactions and to amend the 'race' subsection regarding pharmacokinetic properties based on the results from the completed studies PROSPER: a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer; and Asian PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide in chemotherapy-naive subjects with progressive metastatic prostate cancer who have failed androgen deprivation therapy; and the updated integrated clinical safety database. The package leaflet is updated accordingly; 2) extension of indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC). As a consequence, sections 4.1 and 5.1 of the SmPC are updated, based on the supportive clinical study results of study MDV3100-14 (PROSPER): a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer; study MDV3100-09 (STRIVE): a multicentre phase 2 study to investigate the safety and efficacy of enzalutamide versus bicalutamide in men with non-metastatic or metastatic castration-resistant prostate cancer; and based on supportive non-clinical data from 7 new reports. The package leaflet and the RMP (version 12.1) are updated accordingly

15.3.10. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0050

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC based on the final clinical study report (CSR) of study EXSCEL (EXenatide Study of Cardiovascular Event Lowering): 'a randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus' in fulfilment of PAM (LEG 009). The package leaflet and the RMP (version 31) are updated accordingly

15.3.11. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - EMEA/H/C/004781/WS1369/0001; TRELEGY ELLIPTA (CAP) - EMEA/H/C/004363/WS1369/0001

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to modify the current approved chronic obstructive pulmonary disease (COPD) therapeutic indication to 'maintenance treatment in adult patients with moderate to severe COPD'. As a consequence, sections 4.1, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 02) are updated accordingly. This is based on the results of study CTT116855: a phase 3, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and

tolerability of the fixed dose triple combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with COPD; as well as study 200812: a phase 3B, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC) in subjects with COPD; and the population pharmacokinetics (PK) report 208059

15.3.12. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/II/0012

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to extend the Maviret (glecaprevir/pibrentasvir) indication to adolescents (from 12 to 18 years of age) with chronic hepatitis C infection, based on new clinical data from study M16-123: an open-label, multicentre study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric subjects with genotypes 1-6 chronic hepatitis C virus infection (DORA), using the adult co-formulated tablets in adolescents. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) in line with revision 2 of the guidance on the format of RMP in the EU (template) are updated accordingly

15.3.13. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/X/0083/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 100 mg/ml solution for injection for paediatric use; 2) extension of indication to include paediatric patients from the age of 2 years and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with Simponi (golimumab) 100 mg/mL solution for injection. As a consequence, sections 4.1, 4.2, 5.1 and section 4.1 of the 50mg strength are updated; 3) update of the RMP (version 18.0) to delete the following safety concerns: vasculitis, psoriasis (new onset or worsening of pre-existing), and sarcoidosis/sarcoid like reaction as requested in the outcome of variation II/068/G concluded in May 2016; 4) update of the RMP (version 18.0) to change the due date of study MK-8259-050 (listed as a category 3 study in the RMP) as requested by CHMP in the conclusion of MEA 033 dated April 2017. Finally, the MAH took the opportunity to update the product information in line with the latest QRD template (version 10) to implement the recommendations stated in the revised Annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regard to the excipient sorbitol (E420); to add a statement in section 4.4 of the SmPC to record the name and the batch number of the administered product in line with GVP Module P.II on 'Biological medicinal products' (EMA/168402/2014 Corr*)

15.3.14. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0214

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of Annex II-D of the product information to remove the educational material

for health care professionals. As a consequence, the RMP (version 17.0) is updated. In addition, the MAH took the opportunity to update the package leaflet with some missing warnings and adverse drug reactions (ADRs) already reflected in the SmPC, as requested by CHMP, and to introduce some minor QRD related changes

15.3.15. Insulin aspart - NOVOMIX (CAP) - EMEA/H/C/000308/II/0095

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.5 and 5.1 of the SmPC to include data on the use of NovoMix 30 combination use with glucagon-like peptide 1 (GLP-1) receptor agonists. The package leaflet and the RMP (version 3) are updated accordingly

15.3.16. Insulin glargine - TOUJEO (CAP) - EMEA/H/C/000309/II/0105/G

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations to introduce a new 3 mL pre-filled pen. As a consequence, Annex A, I, IIA and IIIB are amended. In addition, the RMP (version 5.0) in line with revision 2 of the guidance on the format of RMP in the EU (template) is updated accordingly

15.3.17. Insulin human - RYZODEG (CAP) - EMEA/H/C/002499/II/0028

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC based on new clinical data from cardiovascular outcome trial EX1250-4080 (DEVOTE): a randomised, double-blind and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of insulin degludec versus insulin glargine (100 units/mL) in patients with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular events. Based on the long-term exposure and safety data from DEVOTE which are also relevant for insulin degludec/insulin aspart, the product information for Ryzodeg (insulin human) is updated with data from the trial in alignment with a recent update of the product information for insulin degludec-containing product(s). Section 6.5 of the SmPC is also amended to introduce editorial changes relating to the plunger stopper. The RMP (version 7) is updated accordingly

15.3.18. Irinotecan hydrochloride trihydrate - ONIVYDE (CAP) - EMEA/H/C/004125/II/0008, Orphan

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: David Olsen

Scope: Update of sections 1, 2, 4.2, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC in order to reflect the expression of strength based on irinotecan anhydrous free-base. The labelling, package leaflet and the RMP (version 2.1) are updated accordingly. In addition the MAH took the opportunity to introduce minor editorial changes

15.3.19. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/II/0069, Orphan

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene for Kalydeco (ivacaftor) 50 mg and 75 mg granules. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to Kalydeco (ivacaftor) 150 mg film-coated tablet product information. The package leaflet and the RMP (version 7.2) are updated accordingly

15.3.20. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0034/G

Applicant: Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) extension application to introduce a new pharmaceutical form (granules) in 2 strengths (100/125 mg and 150/188 mg) for paediatric use from 2 to 5 years. The RMP (version 4.0) is updated accordingly; 2) update of sections 4.1, 4.2, 4.5, 4.8 and 5.3 of the SmPC of the tablet formulations to bring it in line with the proposed paediatric 2-5 year old extension application

15.3.21. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0021, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of section 4.8 of the SmPC in order to include ‘myocardial infarction’ as a new adverse drug reaction with a frequency ‘uncommon’ in order to fulfil LEG 004.1, following the assessment of PSUSA procedure (PSUSA/00010319/201704) finalised at the November 2017 PRAC meeting. The package leaflet and the RMP (version 6.0) in line with revision 2 of the guidance on the format of RMP in the EU (template) are updated accordingly

15.3.22. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to include information on vaccination based on interim results from study BN29739 (listed as a category 3 study in the RMP): a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of multiple sclerosis (MS). The package leaflet and the RMP (version 2.0) are updated accordingly

15.3.23. Octocog alfa - ADVATE (CAP) - EMEA/H/C/000520/II/0092

Applicant: Baxter AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.1 of the SmPC in order to add new data on immune tolerance induction (ITI) following the final results from study PASS-INT-004: a prospective, multicentre, uncontrolled, open-label, non-interventional post-authorisation safety surveillance study conducted to evaluate Advate (octocog alfa) in ITI therapy in subjects with moderate or severe haemophilia A (baseline factor VIII (FVIII) ≤ 2%) and a high titre (> 5 Bethesda units (BU)) inhibitor to FVIII. The RMP (version 16.0) is updated accordingly

15.3.24. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0136

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 to guide prescribers on the use of Tamiflu (oseltamivir) for treatment in immunocompromised (IC) patients based on study NV20234: a phase 3, double-blind, randomized, stratified, multicentre study of conventional and double dose oseltamivir for the treatment of influenza in IC patients. The package leaflet and RMP (version 18) are updated accordingly. In addition, the MAH took the opportunity to correct some minor errors

15.3.25. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0016/G

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC with the final results from 2 studies, namely: 1) study DFCI 11-001 (listed as a category 3 study in the RMP): a phase 2, open-label, randomized, multicentre study to determine the safety and feasibility of administering an investigational asparaginase product (asparaginase formulation) compared with Oncaspar (pegaspargase) in subjects aged 1 to <22 years with newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma; 2) study AALL07P4 (listed as a category 3 study in the RMP): a multicentre, open label, randomized, active-controlled, parallel design clinical pilot study conducted to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy of an investigational asparaginase product in comparison with Oncaspar (pegaspargase) in patients aged 1 to <31 years newly diagnosed with high risk B-precursor ALL. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.26. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0046

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning and safety information on ‘anaphylaxis’. The RMP (version 3.2) is updated accordingly

15.3.27. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - EMEA/H/C/001104/II/0161

Applicant: Pfizer Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report from effectiveness study B1851041: a phase 4 post marketing study to determine 'national trends in ambulatory care visits for otitis media in children under the age of five in the United States'. The RMP (version 12) is updated accordingly

15.3.28. Prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) - AFLUNOV (CAP) - EMEA/H/C/002094/II/0044/G

Applicant: Seqirus S.r.l

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of an update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC following the completion of clinical study reports for 1) study V87_25: a phase 3, prospective, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59 when administered to subjects with and without underlying medical conditions; 2) study V87_26: a phase 3, prospective, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59 when administered to adults and elderly subjects with immunosuppressive disorders. The package leaflet, labelling and RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to implement some amendments to the product information and introduce some additional minor editorial corrections

15.3.29. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0003/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) update of section 5.2 of the SmPC in order to reflect on results from study CLEE011A2109: a phase 1, open label, multicentre, parallel cohort, single dose study to evaluate the pharmacokinetics (PK) of ribociclib (LEE011) in healthy subjects with normal hepatic function and subjects with impaired hepatic function; 2) update of section 4.2 and 5.2 of the SmPC in order to reflect on results from study CLEE011A2116-Part I: a phase 1, open label, multicentre, parallel-group, single dose two-staged study to evaluate the pharmacokinetics and safety of a single 400 mg oral dose of ribociclib (LEE011) in subjects with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function. The RMP (version 2.0) is updated accordingly

15.3.30. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0004

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist for Kisqali (ribociclib). This is based on data from: 1) study CLEE011E2301: a phase 3 randomized, double-blind, placebo-controlled study of ribociclib (LEE011) or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer and; 2) study CLEE011F2301: a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and to make an administrative update to the Estonian and Latvian local representatives addresses in the package leaflet

15.3.31. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0152

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2 and 4.4 of the SmPC following the submission of the final study report for the non-interventional drug utilisation study (DUS) BA28478: MabThera drug utilisation study and patient alert card evaluation in non-oncology patients in Europe: an infusion centre-based approach. Annex II.E is updated to remove the patient alert card as an additional risk minimisation measure for the risks of progressive multifocal leukoencephalopathy (PML) and infections for the non-oncology indications. The package leaflet and the RMP (version 18) are updated accordingly. This submission fulfils FUM-68.1 and FUM-71

15.3.32. Rolapitant - VARUBY (CAP) - EMEA/H/C/004196/II/0007/G

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) update of SmPC section 4.5 regarding interaction with organic cation transporter 1 (OCT1) substrates to reflects results from non-clinical study 17TESAP2R1: an in vitro evaluation of the substrate and inhibitor potential of rolapitant for efflux and update of transporters; 2) update of SmPC section 4.5 regarding interaction with UDP-glucuronosyltransferase (UGT) substrates following the submission of the results from non-clinical studies, namely: study 170594: evaluation of potential UGT inhibition by rolapitant in cryopreserved human hepatocytes and study TSRP/REP/07CRD75486/2017: evaluation of potential rolapitant metabolism by recombinantly expressed human UGT enzymes; 3) update of SmPC section 4.5 following the submission of the results for study 1000-01-001: an open-label, single-dose study to assess the effects of rolapitant (oral) on the pharmacokinetics of caffeine (CYP1A2) in healthy subjects. The RMP (version 1.2) is updated accordingly

15.3.33. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0001, Orphan

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include a new indication for Rubraca 'as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy'. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated with the expanded clinical efficacy and safety data. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the applicant took the opportunity to propose the move of one paragraph from section 4.4 to 5.1 in the SmPC for consistency with other SmPC agents in this class with this indication

15.3.34. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0033/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include information on dose up-titration for psoriatic arthritis (PsA) and update the radiographic sub-section for PsA based on results from the 24-week data from study CAIN457F2342: a phase 3, randomized, double-blind, placebo controlled multicentre study of subcutaneous secukinumab (150 mg and 300 mg) in prefilled syringe to demonstrate efficacy (including inhibition of structural damage), safety, and tolerability up to 2 years in subjects with active psoriatic arthritis (FUTURE 5), the pooled data from PsA phase 3 studies, the pooled data from patients who up-titrated their secukinumab dose in the following studies, namely: study CAIN457F2306E1: a three-year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active PsA; study CAIN457F2312: efficacy at 24 weeks with long term safety, tolerability and efficacy up to 5 years of secukinumab in patients of active psoriatic arthritis (FUTURE 2) as well as study CAIN457F2318: 24 week efficacy and 3-year safety and efficacy of secukinumab in active psoriatic arthritis, and long-term study observations which demonstrate higher rates of discontinuation for patients on secukinumab 150 mg compared to patients on secukinumab 300 mg. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring it in line with the latest approved SmPC as per procedure IB/0028 finalised in July 2017; 2) the RMP (version 3.0) is updated to include suicidal ideation and behaviour as an important potential risk in the RMP and including minor administrative/editorial changes (LEG 005.2)

15.3.35. Ticagrelor - BRILIQUE (CAP) - EMEA/H/C/001241/II/0042

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.9 and 5.2 of the SmPC in order to update the safety information in relation to renal impairment based on the final results from study D5130L00067: a single dose, randomized, open label, parallel group study conducted to compare the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of

ticagrelor in haemodialysis patients to subjects with normal renal function. The RMP (version 11) is updated accordingly

15.3.36. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0076

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include as a paediatric indication 'treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids' to RoActemra (tocilizumab) 162 mg solution for injection in pre-filled syringe formulation, based on data from phase Ib pharmacokinetic/pharmacodynamic bridging study WA28118 (JIGSAW 118), designed to confirm the RoActemra subcutaneous dosing regimens in patients aged 1 to 17 years old with sJIA, as well as assess the safety of the RoActemra subcutaneous formulation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 24.0) are updated accordingly. In addition, sections 4.2, 4.8 and 5.2 of the SmPC of RoActemra (tocilizumab) 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal intravenous study WA18221 (TENDER): a randomised, placebo-controlled study to evaluate the effect of tocilizumab on disease response in patients with active sJIA

15.3.37. Trastuzumab - HERZUMA (CAP) - EMEA/H/C/002575/II/0006

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new presentation (420 mg/vial) drug product for single-dose, partial use. The strength (concentration after reconstitution) is identical to the previously authorised 150mg/vial presentation. The RMP (version 3.1) is updated accordingly

15.3.38. Vardenafil - LEVITRA (CAP) - EMEA/H/C/000475/WS1390/0062; VIVANZA (CAP) - EMEA/H/C/000488/WS1390/0058

Applicant: Bayer AG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 4.8 of the SmPC to reflect data from two post-marketing observational studies namely: 1) study NCT00759174: 'a study to assess whether phosphodiesterase type 5 inhibitor (PDE5) inhibitors increase the chance of triggering the onset of acute non-arteritic anterior ischaemic optic neuropathy (NAION)', 2) study NCT01131104: 'a study to determine if there is a possible association between NAION and PDE5 inhibitors'; indicating an increased risk of NAION when using PDE5 inhibitors. The MAH also proposed to terminate the NAION study 12912: a prospective case crossover study to assess whether PDE5 inhibitor exposure in men with erectile dysfunction increases the risk for the development of NAION. The RMP (version 5.0) is updated accordingly. In addition, the product information is brought in line with the QRD template (version 10.0) and the contact details of the Bulgarian local representative are updated in the package leaflet. The package leaflets for the 5 mg, 10 mg and 20 mg film-coated tablet strengths

are combined into a single package leaflet and the product information for the 10 mg orodispersible tablet is updated for aspartame and sorbitol, according to the annex to the European Commission (EC) guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Furthermore, the MAH took the opportunity to introduce some editorial amendments to the product information

15.3.39. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0008, Orphan

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include Venclyxto (venetoclax) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. This is based on the results from the MURANO study: a multicentre, phase 3, open-label, randomised study in relapsed/refractory patients with CLL to evaluate the benefit of venetoclax plus rituximab compared with bendamustine plus rituximab. Annex II, the package leaflet and the RMP (version 3.3) are updated accordingly

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

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

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

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

16.1.1. Agomelatine - THYMANAX (CAP); VALDOXAN (CAP) - PSUSA/00000071/201802

Applicant(s): Les Laboratoires Servier (Valdoxan), Servier (Ireland) Industries Ltd. (Thymanax)

PRAC Rapporteur: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.1.2. Albutrepenonacog alfa - IDELVION (CAP) - PSUSA/00010497/201801

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.3. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS (CAP) - PSUSA/00010530/201802

Applicant: MolMed S.p.A, ATMP[99]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.4. Atazanavir, cobicistat - EVOTAZ (CAP) - PSUSA/00010404/201801

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.5. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201802

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.6. Bevacizumab - AVASTIN (CAP); MVASI (CAP) - PSUSA/00000403/201802

Applicant(s): Amgen Europe B.V. (Mvasi), Roche Registration GmbH (Avastin)

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.7. Brentuximab vedotin - ADCETRIS (CAP) - PSUSA/00010039/201802

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.8. Brimonidine[100] - MIRVASO (CAP) - PSUSA/00010093/201802 (with RMP)

Applicant: Galderma International

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.9. Brivaracetam - BRIVIACT (CAP) - PSUSA/00010447/201801

Applicant: UCB Pharma S.A.

[99] Advanced therapy medicinal product
[100] Centrally authorised product(s) only

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Carfilzomib - KYPROLIS (CAP) - PSUSA/00010448/201801

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.11. Ceftazidime, avibactam - ZAVICEFTA (CAP) - PSUSA/00010513/201802

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.12. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201802

Applicant: Actelion Registration Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.13. Cladribine[101] - MAVENCLAD (CAP) - PSUSA/00010634/201801

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.14. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201802

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.15. Colistimethate sodium[102] - COLOBREATHE (CAP) - PSUSA/00009112/201802

Applicant: Teva B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

[101] Indicated in the treatment of multiple sclerosis (MS)
[102] Dry inhalation powder only

16.1.16. Collagenase clostridium histolyticum[103] - XIAPEX (CAP) - PSUSA/00000871/201802

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.17. Dapagliflozin, metformin - EBYMECT (CAP); XIGDUO (CAP) - PSUSA/00010294/201801

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.18. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) - VAXELIS (CAP) - PSUSA/00010469/201802

Applicant: MCM Vaccine B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.19. Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - PSUSA/00010075/201801

Applicants: ViiV Healthcare B.V. (Tivicay), ViiV Healthcare UK Limited (Triumeq)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.20. Elosulfase alfa - VIMIZIM (CAP) - PSUSA/00010218/201802

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.21. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - PSUSA/00010514/201802

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

[103] Indicated in the treatment of Dupuytren's contracture and treatment of Peyronie's disease

16.1.22. Etanercept[104] - BENEPALI (CAP); ERELZI (CAP) - PSUSA/00010452/201801

Applicant(s): Samsung Bioepis UK Limited (Benepali), Sandoz GmbH (Erelzi)

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.23. Etanercept[105] - ENBREL (CAP) - PSUSA/00001295/201802

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.24. Evolocumab - REPATHA (CAP) - PSUSA/00010405/201801

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.25. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201802

Applicant: Chiesi Farmaceutici S.p.A., ATMP[106]

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.26. Fenofibrate, simvastatin - CHOLIB (CAP) - PSUSA/00010096/201802

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.27. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201802

Applicant: Shield TX (UK) Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.28. Florbetaben (^{18}F) - NEURACEQ (CAP) - PSUSA/00010094/201802

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

[104] Biosimilar products only
[105] All products except biosimilar
[106] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.29. Fluticasone, salmeterol[107] - AERIVIO SPIROMAX (CAP); AIREXAR SPIROMAX (CAP) - PSUSA/00010531/201802

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.30. Gimeracil, oteracil monopotassium, tegafur - TEYSUNO (CAP) - PSUSA/00002875/201801

Applicant: Nordic Group B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. Glecaprevir, pibrentasvir - MAVIRET (CAP) - PSUSA/00010620/201801

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.32. Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed) - FENDRIX (CAP) - PSUSA/00001598/201802

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.33. Infliximab[108] - FLIXABI (CAP); INFLECTRA (CAP); REMSIMA (CAP) - PSUSA/00010106/201801

Applicant(s): Celltrion Healthcare Hungary Kft. (Remsima), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis UK Limited (Flixabi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.34. Insulin glargine, lixisenatide - SULIQUA (CAP) - PSUSA/00010577/201801 (with RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

[107] Centrally authorised product(s) only
[108] Biosimilar products only

Scope: Evaluation of a PSUSA procedure

16.1.35. Lenvatinib - LENVIMA (CAP) - PSUSA/00010380/201802

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.36. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/201801

Applicant: CSL Behring GmbH

PRAC Rapporteur: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.1.37. Mercaptamine[109] - CYSTADROPS (CAP) - PSUSA/00010574/201801

Applicant: Orphan Europe SARL

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.38. Modified vaccinia Ankara virus - IMVANEX (CAP) - PSUSA/00010119/201801

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.39. Nilotinib - TASIGNA (CAP) - PSUSA/00002162/201801

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.40. Ospemifene - SENSHIO (CAP) - PSUSA/00010340/201802

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.41. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/201802

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Doris Stenver

[109] Indicated in the treatment of corneal cystine

Scope: Evaluation of a PSUSA procedure

16.1.42. Phenylephrine, ketorolac - OMIDRIA (CAP) - PSUSA/00010419/201801

Applicant: Omeros London Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.43. Pirfenidone - ESBRIET (CAP) - PSUSA/00002435/201802

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.44. Pomalidomide - IMNOVID (CAP) - PSUSA/00010127/201802

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.45. Reslizumab - CINQAERO (CAP) - PSUSA/00010523/201802

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.46. Ribociclib - KISQALI (CAP) - PSUSA/00010633/201802

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.47. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201802

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.48. Ruxolitinib - JAKAVI (CAP) - PSUSA/00010015/201802 (with RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.49. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/201801

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.50. Safinamide - XADAGO (CAP) - PSUSA/00010356/201802

Applicant: Zambon S.p.A.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.51. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201802

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.52. Silodosin - SILODYX (CAP); UROREC (CAP) - PSUSA/00002701/201801

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.53. Simoctocog alfa - NUWIQ (CAP); VIHUMA (CAP) - PSUSA/00010276/201801

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.54. Telotristat - XERMELO (CAP) - PSUSA/00010639/201802

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.55. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201802

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

16.1.56. Trastuzumab emtansine - KADCYLA (CAP) - PSUSA/00010136/201802

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.57. Ulipristal acetate[110] - ESMYA (CAP) - PSUSA/00009325/201802

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.58. Umeclidinium - INCRUSE ELLIPTA (CAP); ROLUFTA ELLIPTA (CAP) - PSUSA/00010263/201712

Applicant(s): Glaxo Group Ltd (Incruse Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Pregabalin - LYRICA (CAP); PREGABALIN PFIZER (CAP); NAP - PSUSA/00002511/201801

Applicants: Pfizer Europe MA EEIG (Lyrica, Pregabalin Pfizer), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.2. Repaglinide - NOVONORM (CAP); PRANDIN (CAP); NAP - PSUSA/00002618/201712

Applicants: Novo Nordisk A/S (NovoNorm, Prandin), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.2.3. ^{13}C-urea - HELICOBACTER TEST INFAI (CAP); PYLOBACTELL (CAP); NAP - PSUSA/00000006/201801

Applicants: INFAI GmbH (Helicobacter Test INFAI), Torbet Laboratories Limited (Pylobactell), various

PRAC Rapporteur: Jan Neuhauser

[110] Indicated in the treatment of moderate to severe symptoms of uterine fibroids

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Acebutolol (NAP) - PSUSA/00000018/201712

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.2. Altizide, spironolactone (NAP) - PSUSA/00002781/201801

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.3. Amiodarone (NAP) - PSUSA/00000166/201712

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Azelastine (NAP) - PSUSA/00000277/201712

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Bendamustine hydrochloride (NAP) - PSUSA/00003162/201801

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.6. Betahistine (NAP) - PSUSA/00000389/201712

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.3.7. Calcitriol (NAP) - PSUSA/00000495/201801

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.8. Cefprozil (NAP) - PSUSA/00000605/201712

Applicant(s): various

PRAC Lead: Gabriela Jazbec

Scope: Evaluation of a PSUSA procedure

16.3.9. Celecoxib (NAP) - PSUSA/00000616/201712

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.10. Cimicifuga racemosa (L.) Nutt., rhizoma (NAP) - PSUSA/00000755/201801

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Cyproheptadine (NAP) - PSUSA/00000902/201712

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.12. Desmopressin (NAP) - PSUSA/00000964/201712

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.13. Enalapril, nitrendipine (NAP) - PSUSA/00001213/201801

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.14. Famciclovir (NAP) - PSUSA/00001349/201712

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.15. Felodipine (NAP) - PSUSA/00001356/201712

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.16. Felodipine, metoprolol (NAP) - PSUSA/00001357/201712

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.17. Furosemide (NAP) - PSUSA/00001491/201801

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.18. Haemophilus influenzae, klebsiella ozaenae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes, streptococcus viridans vaccine (NAP) - PSUSA/00001582/201712

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.19. Hydrochlorothiazide, ramipril (NAP) - PSUSA/00001660/201801

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.20. Hydrochlorothiazide, spironolactone (NAP) - PSUSA/00001662/201801

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.21. Hypericum perforatum L., herba (NAP) - PSUSA/00001701/201801

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.3.22. Ibutilide (NAP) - PSUSA/00001713/201712

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.23. Landiolol (NAP) - PSUSA/00010570/201802

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.24. Levobupivacaine (NAP) - PSUSA/00001848/201712

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.25. Levonorgestrel, ethinylestradiol; ethinylestradiol[111] (NAP) - PSUSA/00010442/201801

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.26. Lidocaine hydrochloride, phenylephrine hydrochloride, tropicamide (NAP) - PSUSA/00010390/201801

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.3.27. Lormetazepam (NAP) - PSUSA/00001910/201712

Applicant(s): various

PRAC Lead: Daniela Philadelphy

Scope: Evaluation of a PSUSA procedure

16.3.28. Lubiprostone (NAP) - PSUSA/00010290/201801

Applicant(s): various

[111] Combination pack only

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.29. Pseudoephedrine, triprolidine (NAP) - PSUSA/00003047/201712

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.30. Sertindole (NAP) - PSUSA/00002695/201801

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.31. Tetanus vaccine (NAP) - PSUSA/00002910/201801

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.32. Tobramycin[112] [113] (NAP) - PSUSA/00009316/201712

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 027.1

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to LEG 027 [cumulative review of cases of headache, dizziness, and abdominal pain/gastrointestinal (GI) pain from all available sources (post marketing cases, clinical trial data and literature) as requested in the conclusions of PSUSA/00000226/201705 adopted at the December 2017 PRAC] as per the request for supplementary information (RSI) adopted in April 2018

16.4.2. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/LEG 009.1

Applicant: Janssen-Cilag International N.V.

[112] Nebuliser solution only
[113] All medicinal products except Centrally Authorised Products (CAP)

PRAC Rapporteur: Ghania Chamouni

Scope: MAH's response to LEG 009 [cumulative review of cases of hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions from all available sources as requested in the conclusions of PSUSA/00009118/201705 adopted at the December 2017 PRAC] as per the request for supplementary information (RSI) adopted in April 2018

16.4.3. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/LEG 066

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Detailed study report of the retrospective analysis of extended interval dosing (EID) versus standard interval dosing (SID), a proposal for further investigation of efficacy and safety in terms of progressive multifocal leukoencephalopathy (PML) risk reduction with EID relative to SID, and updated pharmacokinetic/pharmacodynamic (PK/PD) modelling taking into account body weight and extended dosing intervals, as requested in the conclusions of PSUSA/00002127/201708 adopted by PRAC in March 2018

16.4.4. Regorafenib - STIVARGA (CAP) - EMEA/H/C/002573/LEG 011

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Cumulative review of cases of 'necrotising fasciitis' (NF) from all sources as requested in the conclusions of PSUSA/00010133/201709 adopted by PRAC in April 2018

16.4.5. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/LEG 036

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Cumulative review and analysis of cases of progressive multifocal leukoencephalopathy (PML) reported in patients treated with thalidomide as requested in the conclusions of PSUSA/00002919/201710 adopted by PRAC in May 2018

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)[114]

None

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

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[115]

17.2.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 016

Applicant: Bayer AG

PRAC Rapporteur: Ghania Chamouni

Scope: Protocol for a follow-up survey measuring the effectiveness of the updated educational material for healthcare professionals (HCPs): a survey to investigate whether physicians have received the revised educational materials, measuring physician knowledge and understanding of the key information in the revised educational materials, and whether physicians have provided the patient booklet to their patients [result due date expected within 6 months after completion of the survey] (from variation II/39 finalised in April 2018)

17.2.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/MEA 002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Protocol for study BO40643: a survey measuring the effectiveness of the risk minimisation activities to prescribers: correct implementation of Alecensa (alectinib) label guidance by prescribers of the following important identified risks: interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia and creatine phosphokinase (CPK) elevations (from variation II/01 finalised in October 2017)

17.2.3. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Protocol for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings (from initial MAA/opinion)

17.2.4. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.2

Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 001 [protocol for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; final study report expected within a year of availability of the final data set] (from initial MAA/opinion)] as per the request for supplementary information (RSI) adopted in March 2018

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

17.2.5. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 002.1

Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 002 [protocol for study M-41008-44: a PASS retrospective chart review to assess the effectiveness of Skilarence (dimethyl fumarate) risk minimisation activities in daily practice] as per the request for supplementary information (RSI) adopted in March 2018

17.2.6. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/MEA 006.4

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 006.3 [protocol for drug utilisation study (DUS) ELIGL C06912 conducted in the US population using the MarketScan database to assess adherence to the labelling with regard to drug-drug interactions (DDI) and to genotyping assessment prior to the initiation of eliglustat therapy] as per the request for supplementary information (RSI) adopted in March 2018

17.2.7. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/MEA 005.2

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA005.1 [protocol for a non-imposed, non-interventional PASS safety study: a drug utilisation study (DUS) of Intuniv (guanfacine extended release) in European countries (DUS-database) and protocol for a prescriber survey (DUS-survey) conducted in European countries] as per the request for supplementary information (RSI) adopted in April 2018

17.2.8. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 002.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002.1 [protocol for a study/survey (listed as a category 3 study in the RMP): a cross-sectional multinational, multichannel survey conducted among healthcare professionals and patients to measure the effectiveness of Suliqua (insulin glargine/lixisenatide) educational materials set up to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide] as per the request for supplementary information (RSI) adopted in March 2018

17.2.9. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.2

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 001.1 [protocol for study A-LUT-T-E02-402 (SALUS study, listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (^{177}Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs)] as per the request for supplementary information (RSI) adopted in April 2018

17.2.10. Mercaptamine - CYSTADROPS (CAP) - EMEA/H/C/003769/MEA 001.2

Applicant: Orphan Europe SARL

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 001.1 [PASS protocol for study CYT-DS-001 (listed as a category 3 study in the RMP): an open-label longitudinal PASS to assess the safety of Cystadrops (mercaptamine) in paediatric and adult cystinosis patients in long term use [final clinical study report (CSR) due date: by 2021] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted in June 2018

17.2.11. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.5

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 003.4 [protocol for study NB-451: a protocol synopsis for an observational retrospective database study based on secondary data analysis using existing databases, as suitable] as per the request for supplementary information (RSI) adopted in April 2018

17.2.12. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/MEA 067

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study IMA-06-02: the TOP study (Tysabri Observational Programme): an open label, multinational, multicentre, prospective, observational study to address the long-term safety profile and long-term impact on disease activity and progression of natalizumab with marketed use, and the impact of treatment on disability in particular by comparing the results with prospectively determined controls from established databases

17.2.13. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 004

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Protocol for study BA39730 (listed as a category 3 study in the RMP): a long term surveillance study to assess and characterize the long-term safety data from the use of ocrelizumab in treated patients with multiple sclerosis (MS) [final report due date expected in 12/2028] (from initial MA/opinion)

17.2.14. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/MEA 002.1

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 [PASS protocol for a safety surveillance programme using existing EU rheumatoid arthritis (RA) registries conducted in four countries: Germany (German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (OBS15180)), Spain (Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER) (6R88-RA-1720)), Sweden (Register for Antirheumatic Therapies in Sweden (ARTIS) (OBS15220)) and UK (British Society for Rheumatology Biologicals Register (BSRBR) (6R88-RA-1634)) (from initial MAA/opinion)] as per the request for supplementary information (RSI) adopted in March 2018

17.2.15. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in users of Ozempic (semaglutide) [final study report expected 5 years after start of study] (from initial MA/opinion)

17.2.16. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/MEA 008

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a study to evaluate the effectiveness of risk minimisation measures (RMM): a survey among healthcare professionals to assess their knowledge on dosing and administration of Obizur (susoctocog alfa) in six European countries

17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 007.1

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007 [protocol for a non-interventional PASS study A3921298 (listed as a category 3 study in the RMP) evaluating the effectiveness of additional risk minimisation measures (aRMM) for Xeljanz (tofacitinib) in the European Union via a survey of healthcare professionals (HCPs) considered as an additional pharmacovigilance activity in the RMP] as per the request for supplementary information (RSI) adopted in April 2018

17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 008

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study A3921312 (listed as a category 3 study in the RMP): a

prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)

17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 009

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study A3921314 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Swedish (ARTIS) register

17.2.20. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 010

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study A3921316 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the Spanish registry of adverse events of biological therapies and biosimilars in rheumatoid diseases (BIOBADASER)

17.2.21. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 011

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for study A3921317 (listed as a category 3 study in the RMP): a prospective non-interventional comparative active surveillance PASS of serious infection, malignancy, cardiovascular and other adverse event rates among patients treated with Xeljanz (tofacitinib) for moderately to severely active rheumatoid arthritis (RA) within the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

17.2.22. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 025.3

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Amendment to protocol version 4 previously agreed in September 2017 as part of MEA 025.2, to evaluate the effectiveness of risk minimisation measures: a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of Vpriv (velaglucerase alfa) relating to the risk of serious hypersensitivity/allergic reactions

17.3. Results of PASS imposed in the marketing authorisation(s)[116]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[117]

17.4.1. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0058

Applicant: Pfizer Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of the final study report for study A8081038 (listed as a category 3 study in the RMP): a multinational active safety surveillance study of crizotinib in Europe and the United States to evaluate safety outcomes among lung cancer patients

17.4.2. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1270/0216; LIFMIOR (CAP) - EMEA/H/C/004167/WS1270/0013

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final report from study B1801396 (listed as a category 3 study in the RMP): a non-interventional, population-based, multi-country, observational cohort register study to evaluate the risk of adverse pregnancy outcomes in patients with rheumatoid arthritis and related inflammatory diseases, who were treated with etanercept compared to patients with the same diseases of interest who were treated with non-biologic systemic drugs, but without etanercept or other biologics during pregnancy, using merged data from Sweden, Denmark and Finland

17.4.3. Everolimus - VOTUBIA (CAP) - EMEA/H/C/002311/II/0055, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from non-interventional study CRAD001MIC03 (listed as a category 3 study in the RMP): an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex

17.4.4. Prucalopride - RESOLOR (CAP) - EMEA/H/C/001012/II/0042

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final clinical study report (CSR) for the post-authorisation drug utilisation study (DUS) SHP555-804 (in fulfilment of MEA 006.11): a DUS to examine characteristics of patients prescribed Resolor (prucalopride) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy

[116] In accordance with Article 107p-q of Directive 2001/83/EC
[117] 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

outcomes in the UK clinical practice research datalink (CPRD) database. The RMP (version 14.0) is updated accordingly

17.4.5. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0186

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study GS-EU-174-1846 (listed as a category 3 study in the RMP, in fulfilment of MEA 273): a multicentre, non-interventional, retrospective, matched cohort study of patients mono-infected with chronic hepatitis B and with moderate or severe renal impairment treated with Viread (tenofovir disoproxil) or entecavir

17.4.6. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/II/0188

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study GS-EU-174-0224 (listed as a category 3 study in the RMP): a cross-sectional drug utilisation study (DUS) in children and adolescents with chronic hepatitis B (CHB) to assess whether physicians prescribing Viread (tenofovir disoproxil) to paediatric patients with CHB in the EU follow the relevant recommendations in the SmPC and educational brochures

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation[118]

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.6

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 007.5 [third annual report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)] as per the request for supplementary information (RSI) adopted in May 2018

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.9

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 024.8 [annual report for the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at

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

collecting immunological data, and follow-up growth disturbances in children] as per the request for supplementary information (RSI) adopted in April 2018

17.5.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 053.6

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: MAH's response to MEA 053.5 [second interim study report for PASS study ALGMYC07390 evaluating the prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions, including MAH's response to MEA 053.4 on first interim report as per the request for supplementary information adopted in July 2017 [final clinical study report (CSR): due 31 August 2019] as per the request for supplementary information (RSI) adopted in March 2018

17.5.4. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 006.3

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Interim results for the UK clinical practice research datalink (CPRD) database data analysis for psoriatic arthritis (PsA) and psoriasis [due date: CPRD data analysis at years 1, 3 and 5 starting from the date of first commercial availability in the UK. Final study report due for submission within 6 months after the 5 year-data analysis cut-off date]

17.5.5. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.3

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Menno van der Elst

Scope: Three year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in: April 2023]

17.5.6. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 007

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Interim study result for study 109MS401 (ESTEEM study): a multicentre, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of relapsing multiple sclerosis [final clinical study report (CSR) expected due date: Q4/2024]

17.5.7. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/MEA 008

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Annual progress report (version 2.0) for study 109MS402: Biogen multiple sclerosis pregnancy exposure registry [final clinical study report (CSR) expected due date: Q4 2021]

17.5.8. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 005.2

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: Second interim results for study FBB-01_02_13: a prospective observational study to assess the effectiveness of the training and risk minimisation measures recommended for the usage of the diagnostic agent Neuraceq (florbetaben (^{18}F)) in post-authorisation clinical settings [final clinical study report (CSR) expected due date: Q1/2019]

17.5.9. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 007.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final report expected by May 2026] and MAH's response to MEA 007.2 as per the request for supplementary information (RSI) adopted in September 2017

17.5.10. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 010.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) [final report expected by May 2026] and MAH's response to MEA 010.2 as per the request for supplementary information (RSI) adopted in September 2017

17.5.11. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 007.3

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Remsima (infliximab) in patients with rheumatoid arthritis (EU and Korea) [final report expected by May 2026] and MAH's response to MEA 007.2 as per the request for supplementary information (RSI) adopted in September 2017

17.5.12. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 010.3

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Annual interim safety and efficacy report for registry CT-P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra (infliximab) in patients with Crohn's disease (CD), and ulcerative colitis (UC) (EU and Korea) [final report expected by May 2026] and MAH's response to MEA 010.2 as per the request for supplementary information (RSI) adopted in September 2017

17.5.13. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.9

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual interim report for the passive enhanced safety surveillance study (ESS) D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2017-2018 influenza season in England

17.5.14. Liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/MEA 015.2

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Interim results for study NN8022-4246: a drug utilisation study (DUS) in the UK using UK clinical practice research datalink (CPRD) database evaluating if liraglutide (Saxenda) is used according to approved indication and posology and if liraglutide (Victoza) is used for weight management

17.5.15. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.6

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 017.5 [first interim report for study V72_36OB: a post-licensure observational safety study after Bexsero (meningococcal B vaccine 4CMenB) vaccination in routine UK care [final report due date: 31/12/2019]] as per the request for supplementary information (RSI) adopted in April 2018

17.5.16. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/MEA 017.7

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth progress report for study V72_36OB: a post-licensure observational safety study after Bexsero (meningococcal B vaccine 4CMenB) vaccination in routine UK care [final report due date expected in December 2019]

17.5.17. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Interim results for epidemiological study 15689: an evaluation of adverse events of special interest (AESI) in the PEDiatric NETwork (PedNet) haemophilia registry (from MA/opinion)

17.5.18. Ospemifene - SENSHIO (CAP) - EMEA/H/C/002780/ANX 001.5

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Third annual interim report for a PASS (ENCEPP/SDPP/8585) (listed as a category 1 in the RMP): an observational retrospective cohort study of ospemifene utilising existing databases in Germany, Italy, Spain, and the United States to evaluate the incidence of venous thromboembolism and other adverse events in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERM) for oestrogen-deficiency conditions or breast cancer prevention and; 2) the incidence in untreated VVA patients [final report expected in February 2021]

17.5.19. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 023.4

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim results for study 16167 (Wave 2): a risk minimisation study/survey evaluating the adherence to the prescriber's guide on deep vein thrombosis treatment (DVT-T) and stroke prevention in atrial fibrillation (SPAF) indication

17.5.20. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/ANX 002.6

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Second interim results for PASS D7120R00003 (previously RO-2455-403-RD): a long-term post-marketing observational study exploring the safety of roflumilast in the treatment of chronic obstructive pulmonary disease (COPD), combined data results from Sweden, Germany and the US (Annex II-D condition) [final clinical study report (CSR) expected in March 2021]

17.5.21. Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.3

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 004.2 [annual progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the

long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]] as per the request for supplementary information (RSI) adopted in April 2018

17.5.22. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.2

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 004.1 [annual progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]] as per the request for supplementary information (RSI) adopted in April 2018

17.5.23. Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/MEA 011.4

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Fifth annual interim report for study H4621g (MotHER pregnancy register): an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin (trastuzumab), pertuzumab in combination with Herceptin, or pertuzumab during pregnancy or within 7 months prior to conception [final report expected in May 2024]

17.5.24. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.14

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 022.13 [annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics] as per the request for supplementary information (RSI) adopted in April 2018

17.5.25. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 023.10

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Eighth annual interim report for study CNTO1275PSO4005 (Nordic database initiative): a prospective cohort registry, five-year observational study of adverse events (AEs) observed in patients exposed to ustekinumab

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 009.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Updated feasibility assessment within 2 years (e.g. by Q2/2018) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using 3 EU databases (United Kingdom, Spain and Italy) on market uptake and exposure within the UK, Spain and Italy

17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 008.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Updated feasibility assessment within 2 years (e.g. by Q2/2018) to evaluate the drug utilisation patterns of canagliflozin-containing medicines including off-label usage in type 1 diabetes mellitus (T1DM) and the risk of diabetic ketoacidosis (DKA) using 3 EU databases (United Kingdom, Spain and Italy) on market uptake and exposure within the UK, Spain and Italy

17.6.3. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/MEA 024.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 024 [signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia (EPITT 18688) to review the instructions for use (IFU) for Bydureon (exenatide) and propose improvements of the IFU as applicable] as per the request for supplementary information (RSI) adopted in March 2018

17.7. New Scientific Advice

None

17.8. Ongoing Scientific Advice

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

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

None

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

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

18.1. Annual reassessments of the marketing authorisation

None

18.2. Conditional renewals of the marketing authorisation

None

18.3. Renewals of the marketing authorisation

18.3.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/R/0040 (with RMP)

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

18.3.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/R/0042 (with RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

18.3.3. Brimonidine - MIRVASO (CAP) - EMEA/H/C/002642/R/0021 (without RMP)

Applicant: Galderma International

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/R/0024 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.5. Florbetaben (^{18}F) - NEURACEQ (CAP) - EMEA/H/C/002553/R/0025 (with RMP)

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.6. Follitropin alfa - BEMFOLA (CAP) - EMEA/H/C/002615/R/0019 (without RMP)

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.7. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/R/0079 (with RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.8. Japanese encephalitis vaccine (inactivated, adsorbed) - IXIARO (CAP) - EMEA/H/C/000963/R/0091 (without RMP)

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.9. Levetiracetam - LEVETIRACETAM HOSPIRA (CAP) - EMEA/H/C/002783/R/0018 (with RMP)

Applicant: Hospira UK Limited

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.10. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/R/0020 (with RMP)

Applicant: Aziende Chimiche Riunite Angelini Francesco S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.11. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0009 (without RMP)

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/R/0128 (without RMP)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.13. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/R/0026 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.14. Travoprost - IZBA (CAP) - EMEA/H/C/002738/R/0011 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.15. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/R/0032 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.16. Vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/R/0019 (with RMP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.17. Zoledronic acid - ZOLEDRONIC ACID ACCORD (CAP) - EMEA/H/C/002667/R/0006 (without RMP)

Applicant: Accord Healthcare Limited

PRAC Rapporteur: Doris Stenver

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 03-06 September 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Daniela Philadelphy	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 7.3.2. Magnesium

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				sulphate heptahydrate, sodium sulphate anhydrous, potassium sulphate (NAP) - EMEA/H/N/PSR/S/0016
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.3.5. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP),

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP) 4.3.7. Olanzapine – ZALASTA (CAP) - EMEA/H/C/000792/SDA/006, ZYPADHERA (CAP) - EMEA/H/C/000890/SDA/028, ZYPREXA (CAP) - EMEA/H/C/000115/SDA/049, ZYPREXA VELOTAB (CAP) - EMEA/H/C/000287/SDA/042; NAP Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Krka d.d. (Zalasta), various PRAC Rapporteur: Kimmo Jaakkola EMA resources: SML: Cosimo Zaccaria; PM: Marine Bunch; EPL: Florence Butlen-Ducuing Scope: Signal of somnambulism EPITT 19202 – Follow-up to April 2018 4.3.9. Sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/SDA/037,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				RISTABEN (CAP) - EMEA/H/C/001234/SDA/015, TESAVEL (CAP) - EMEA/H/C/000910/SDA/031, XELEVIA (CAP) - EMEA/H/C/000762/SDA/036; sitagliptin, metformin hydrochloride – JANUMET (CAP) - EMEA/H/C/000861/SDA/019, EFFICIB (CAP) - EMEA/H/C/000896/SDA/019, RISTFOR (CAP) - EMEA/H/C/001235/SDA/015, VELMETIA (CAP) - EMEA/H/C/000862/SDA/019 Angiotensin-converting-enzyme (ACE)-inhibitors: benazepril (NAP); captopril (NAP); cilazapril (NAP); delapril (NAP); enalapril (NAP); fosinopril (NAP); imidapril (NAP); lisinopril (NAP); moexipril (NAP); perindopril (NAP); quinapril (NAP); ramipril (NAP); spirapril (NAP); trandolapril (NAP); zofenopril (NAP); zofenopril, hydrochlorothiazide (NAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Anne-Cécile Vuillemin	Alternate	Luxembourg	No restrictions applicable to this meeting	Full involvement
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.2.7. Rivaroxaban – XARELTO (CAP) 4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 4.3.5. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP) 4.3.9. Sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/SDA/037, RISTABEN (CAP) - EMEA/H/C/001234/SDA/015, TESAVEL (CAP) - EMEA/H/C/000910/SDA/031, XELEVIA (CAP) - EMEA/H/C/000762/SDA/036;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				sitagliptin, metformin hydrochloride – JANUMET (CAP) - EMEA/H/C/000861/SDA/019, EFFICIB (CAP) - EMEA/H/C/000896/SDA/019, RISTFOR (CAP) - EMEA/H/C/001235/SDA/015, VELMETIA (CAP) - EMEA/H/C/000862/SDA/019 Angiotensin-converting-enzyme (ACE)-inhibitors: benazepril (NAP); captopril (NAP); cilazapril (NAP); delapril (NAP); enalapril (NAP); fosinopril (NAP); imidapril (NAP); lisinopril (NAP); moexipril (NAP); perindopril (NAP); quinapril (NAP); ramipril (NAP); spirapril (NAP); trandolapril (NAP); zofenopril (NAP); zofenopril, hydrochlorothiazide (NAP) 6.3.10. Amitriptyline (NAP); amitriptyline, amitriptylinoxide (NAP); amitriptylinoxide (NAP) - PSUSA/00010374/201801 6.3.36. Levonorgestrel

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP) - PSUSA/00001856/201712 11.1.2. Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); prulifloxacin (NAP); rufloxacin (NAP)
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Expert - via telephone*	Belgium	No interests declared	Full involvement
Benjamin Burrus	Expert - via telephone*	France	No interests declared	Full involvement
Annabelle Page	Expert - via telephone*	France	No interests declared	Full involvement
Véronique Tonnay	Expert - via telephone*	France	No interests declared	Full involvement
Nicole Bick	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Loeschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Emma Christina Lawless	Expert - in person*	Ireland	No interests declared	Full involvement
Liana Gross-Martirosyan	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Sara Khosrovani	Expert - in person*	Netherlands	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Kristin Thorseng Kvande	Expert - in person*	Norway	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Bolin	Expert - via telephone*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth	Expert - via telephone*	Sweden	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
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwyini	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anna Vikerfors	Expert - via telephone*	Sweden	No interests declared	Full involvement
Andrew Ruddick	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

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

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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