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SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 5-8 October 2015

Chair: June Raine – Vice-Chair: Almath Spooner

### **Health and safety information**

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

### **Disclaimers**

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

Of note, these 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 ongoing procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).



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## 1. Introduction

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

The Chairperson opened the 5-8 October 2015 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 II18. ). 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 noted that Artūras Kažemekaitis stepped down from his position of alternate for Lithuania and thanked him for his contribution.

### 1.2. Adoption of agenda of the meeting on 5-8 October 2015

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

### 1.3. Adoption of the minutes of the previous meeting on 7-10 September 2015

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 7-10 September 2015 were published on the EMA website on 30 October 2015 ([EMA/PRAC/722174/2015](#)).

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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

### 2.3. Procedures for finalisation

None

### 2.4. Planned public hearings

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

- 3.2.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)  
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP)  
Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) – GARDASIL 9 (CAP) - EMEA/H/A-20/1421

MAH(s): GlaxoSmithKline Biologicals S.A. (Cervarix), Sanofi Pasteur MSD SNC (Gardasil, Gardasil 9), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Julie Williams; PRAC Co-rapporteurs: Jean-Michel Dogné, Qun-Ying Yue

Scope: Review to further clarify the safety profile of human papillomavirus vaccines following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

#### Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing to further clarify the safety profile of Cervarix, Gardasil, Gardasil 9 and Silgard (human papillomavirus vaccines) in relation to the available data regarding complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). For background information, see [PRAC minutes July 2015](#) and [PRAC minutes September 2015](#).

#### Summary of recommendation(s)/conclusions

The PRAC agreed on a list of questions to the Scientific Advisory Group on Vaccines (SAG-V) scheduled on 21 October 2015 and endorsed the list of experts for the SAG-V.

### 3.2.2. Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Carmela Macchiarulo

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

### **Background**

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for the review of Tysabri (natalizumab). For background information, see [PRAC minutes May 2015](#) and [PRAC minutes September 2015](#).

### **Summary of recommendation(s)/conclusions**

The PRAC discussed the possibility to consult selected multiple sclerosis registries in the European Union in order to gather further information on the collection of cases of progressive multifocal leukoencephalopathy (PML). The PRAC agreed a list of questions (LoQ) and to inviting the registries to respond in accordance with a revised timetable ([EMA/PRAC/293314/2015 rev2](#)).

- 3.2.3. Sodium-glucose co-transporter-2 (SGLT2) inhibitors:  
canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP);  
dapagliflozin – FORXIGA (CAP); dapagliflozin, metformin – XIGDUO (CAP);  
empagliflozin - JARDIANCE (CAP); empagliflozin, metformin – SYNJARDY (CAP) -  
EMA/H/A-20/1419
- 

Applicant: AstraZeneca AB (Forxiga, Xigduo), Boehringer Ingelheim International GmbH (Jardiance, Synjardy), Janssen-Cilag International N.V. (Invokana, Vokanamet)

PRAC Rapporteur: Menno van der Elst; PRAC Co-rapporteurs: Valerie Strassmann, Qun-Ying Yue

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

### **Background**

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing to review the risk of diabetic ketoacidosis (DKA) and its impact on the benefit:risk balance of sodium-glucose co-transporter-2 (SGLT2) inhibitor medicinal products containing canagliflozin, dapagliflozin and empagliflozin alone or in combination with metformin. For background information, see [PRAC minutes June 2015](#).

### **Summary of recommendation(s)/conclusions**

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable ([EMA/PRAC/391289/2015 rev. 1](#)).

## **3.3. Procedures for finalisation**

None

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

None

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>1</sup>

### 4.1. New signals detected from EU spontaneous reporting systems

#### 4.1.1. Adalimumab – HUMIRA (CAP)

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Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA)  
EPITT 18447– New signal  
Lead Member State: SE

#### Background

Adalimumab is a selective immunosuppressive agent indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease and ulcerative colitis under certain conditions.

The exposure for Humira, a centrally authorised medicine containing adalimumab, is estimated to have been more than 2.9 million patients-years worldwide, in the period from first authorisation in 2003 up to December 2013.

Following the publication<sup>2</sup> of a well-documented case of autoimmune haemolytic anaemia (AIHA) after 3 years of treatment with adalimumab for plaque psoriasis, a signal of AIHA and haemolytic anaemia (HA) was identified by the EMA, based on 12 supportive cases of AIHA or HA retrieved from EudraVigilance (including one case reported in the literature). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account that positive de-challenge was observed in 4 out of 12 cases, that cases of AIHA have also been reported in patients treated with adalimumab for indications other than

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<sup>1</sup> 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

<sup>2</sup> Harada Y, et al. Autoimmune hemolytic anemia during adalimumab treatment for plaque psoriasis. Intern Med. 2015;54(9):1103-4



rheumatoid arthritis and that the authors of the well-documented case of AIHA suggested an underlying biological mechanism, the PRAC agreed to request the MAH for Humira to provide a cumulative review of cases of AIHA and of HA, including the published literature and data from clinical trials.

#### **Summary of recommendation(s)**

- The MAH for Humira (adalimumab) should submit to the EMA, within 60 days, a cumulative review of cases of AIHA, including the published literature and data from clinical trials. Cases of HA should be included in the review in consideration of the potential for misclassification of AIHA as HA. The MAH should discuss the possible causal relationship and biological plausibility, as well as the need for any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.2. Carbidopa, levodopa (NAP)**

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Applicant: AbbVie Ltd, various

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of intussusception

EPITT 18424 – New signal

Lead Member State: SE

#### **Background**

Levodopa is a metabolic precursor of the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) collectively known as catecholamines. Carbidopa is a peripheral levodopa/dopa decarboxylase (DDC) inhibitor which reduces the peripheral metabolism of levodopa to dopamine, and thus, more levodopa is available to the brain. Levodopa in combination with carbidopa as a gel for continuous intestinal infusion is indicated for the treatment of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia/dyskinesia.

During routine signal detection activities, a signal of intussusception associated with the intestinal gel formulation was identified by the EMA, based on 7 cases retrieved from EudraVigilance. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance. Taking into account that all reported cases were serious and that there seems to be an association with de-challenge/re-challenge in some of the reported cases, the PRAC agreed to request the MAH for Duodopa (AbbVie) to provide a cumulative review of cases of intussusception in association with levodopa/carbidopa, including clinical trials, literature and post-marketing experience.

The PRAC appointed Qun-Ying Yue as Rapporteur for the signal.

#### **Summary of recommendation(s)**

- The MAH for Duodopa (levodopa/carbidopa) should submit to the EMA, within 60 days, a cumulative review of cases of intussusception in association with levodopa/carbidopa intestinal gel including clinical trials, literature and post-marketing experience. The MAH should consider all possible causes, including the pharmacological substances, the intestinal gel, and the intestinal tube/catheter. The MAH should also discuss the need for any potential amendment to the product information and/or to the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.1.3. Ibrutinib – IMBRUVICA (CAP)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Signal of peripheral neuropathy

EPITT 18480 – New signal

Lead Member State: UK

##### **Background**

Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK) indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), the treatment of adult patients with chronic lymphocytic leukaemia (CLL) under certain conditions and for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) under certain conditions.

The post-marketing exposure for Imbruvica, a centrally authorised medicine containing ibrutinib, is estimated to have been more than 106,372 patient-months worldwide, in the period from first authorisation in 2014 until April 2015.

During routine signal detection activities, a signal of peripheral neuropathy was identified by the EMA, based on 4 cases of Guillain-Barré syndrome (GBS) and 2 additional cases of acute neuropathy retrieved from EudraVigilance. The Rapporteur confirmed that the signal of peripheral neuropathy needed initial analysis and prioritisation by the PRAC.

##### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and noted that the reported cases do not provide sufficient evidence of a causal association between ibrutinib and GBS. However taking into account the reports of peripheral neuropathy including spontaneous cases and cases reported in the published literature related to the class, the PRAC agreed to request the MAH for Imbruvica to provide a cumulative review of cases of peripheral neuropathy including GBS associated with ibrutinib in clinical trials, literature and from post-marketing experience.

##### **Summary of recommendation(s)**

- The MAH for Imbruvica (ibrutinib) should submit to the EMA, in the next PSUR (DLP: 12/11/2015) (PSUSA/00010301/201511), a cumulative review of cases of peripheral neuropathy including GBS associated with ibrutinib in clinical trials, literature and from

post-marketing experience. Based on this review the MAH should consider the need for updates to the product information as applicable.

#### 4.1.4. Peginterferon alfa-2a – PEGASYS (CAP)

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Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of acquired haemophilia  
EPITT 18476 – New signal  
Lead Member State: SE

##### **Background**

Peginterferon alfa-2a is a conjugate of bis-monomethoxypolyethylene glycol with interferon alfa-2a. Interferon alfa-2a is an endogenous glycoprotein with immunomodulatory, antiviral and antiproliferative properties indicated for the treatment of chronic hepatitis B and of hepatitis C under certain conditions.

The exposure for Pegasys, a centrally authorised medicine containing peginterferon alfa-2a, is estimated to have been around 2,750,000 patients worldwide, in the period from first authorisation in 2002 until July 2014.

During routine signal detection activities, a signal of acquired haemophilia/acquired factor VIII inhibitor was identified by the EMA, based on 17 cases retrieved from EudraVigilance (including 8 cases reported in the literature). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

##### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that 17 cases of acquired haemophilia or factor VIII inhibition have been reported in association with peginterferon alfa-2a, that interferons alfa have been associated with autoimmune disorders, and also that acquired haemophilia is a serious and potentially life-threatening bleeding disorder, the PRAC agreed to request the MAH for Pegasys to provide a cumulative review of cases of acquired haemophilia, factor VIII inhibition and related terms, including data from the literature, clinical development and post-marketing.

##### **Summary of recommendation(s)**

- The MAH for Pegasys (peginterferon alfa-2a) should submit to the EMA, within 60 days, a cumulative review of cases of acquired haemophilia, factor VIII inhibition and related terms, including data from the literature, clinical development and post-marketing. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.1.5. Ustekinumab - STELARA (CAP)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Signal of pemphigoid  
EPITT 18469 – New signal  
Lead Member State: UK

## Background

Ustekinumab is a fully human immunoglobulin (Ig) G1 $\kappa$  monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23, indicated for the treatment of plaque psoriasis, for the treatment of paediatric plaque psoriasis and for the treatment of psoriatic arthritis under certain conditions.

The exposure for Stelara, a centrally authorised medicine containing ustekinumab, is estimated to have been more than 379,596 person-years worldwide, in the period from first authorisation in 2009 until December 2014.

Following the publication<sup>3</sup> of one case of bullous pemphigoid during treatment of psoriatic onycho-pachydermo periostitis with ustekinumab, a signal of pemphigoid was identified by the EMA, based on 10 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that in some cases there was a temporal relationship and a positive de-challenge, the PRAC agreed to request the MAH to provide a cumulative analysis of all the cases of pemphigoid reported in association with the use of ustekinumab.

## Summary of recommendation(s)

- The MAH for Stelara (ustekinumab) should submit to the EMA, within 60 days, a cumulative analysis of all the cases of pemphigoid and related terms reported in association with the use of ustekinumab. Cases arising from clinical and observational studies, spontaneous post-marketing reports and the scientific literature should all be included. The MAH should also discuss the findings of all specialist diagnostic testing performed to clarify the diagnosis in the cases, in relation to commonly agreed histological and biological criteria for the diagnosis of pemphigoid and other bullous conditions. In addition, the MAH should evaluate the possible pathophysiological mechanisms of a role of ustekinumab in the development of pemphigoid and other bullous conditions, and finally consider the need for any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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<sup>3</sup> Nakayama C, Yasuyuki F, Watanabe M et al. Development of bullous pemphigoid during treatment of psoriatic onycho-pachydermo periostitis with ustekinumab. *Journal of dermatology*. 2015; 42:1-3

## 4.2. New signals detected from other sources

### 4.2.1. Alogliptin – VIPIDIA (CAP); alogliptin, metformin – VIPDOMET (CAP); alogliptin, pioglitazone – INCRESYNC (CAP) Linagliptin – TRAJENTA (CAP); linagliptin, metformin – JENTADUETO (CAP)

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Applicant: Boehringer Ingelheim International (Trajenta, Jentaduetto), Takeda Pharma A/S (Vipidia, Vipdomet, Incresync)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of arthralgia  
EPITT 18489 – New signal  
Lead Member State: NL

#### Background

Alogliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Linagliptin is a DPP-4 inhibitor indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as monotherapy and as combination therapy under certain conditions.

The post-marketing exposure for Vipidia, a centrally authorised medicine containing alogliptin, is estimated to have been more than 2,220,671 patient-years worldwide, in the period from first authorisation in 2013 until April 2015. The post-marketing exposure for Incresync, a centrally authorised medicine containing alogliptin in combination with pioglitazone, is estimated to have been more than 418,859 patient-years worldwide from first authorisation in 2013 until April 2015.

The post-marketing exposure for Trajenta, a centrally authorised medicine containing linagliptin, is estimated to have been more than 3,062,378 patient-years worldwide, in the period from first authorisation in 2011 until May 2015. The post-marketing exposure for Jentaduetto, a centrally authorised medicine containing linagliptin in combination with metformin, is estimated to have been more than 581,162 patient-years worldwide from first authorisation in 2012 until May 2015.

Following the issue of a [safety warning by the FDA on DPP-4 inhibitors and the risk of severe joint pain](#) in August 2015, based on 33 cases of cases of severe arthralgia reported in the FDA Adverse Event Reporting System (FAERS) database with the use of DPP-4 inhibitors, a signal of arthralgia was identified by the Netherlands, based on 2 cases retrieved for alogliptin and 19 cases retrieved for linagliptin from EudraVigilance. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that cases of arthralgia and muscle pain have been reported in association with all compounds of the DPP-4 inhibitors class and that this adverse drug reaction is listed for all but linagliptin and alogliptin, the most recently authorised DPP-4 inhibitors, that causality could not be ruled out for 2 cases and that positive de-challenge

was reported in one case and positive re-challenge in another case, the PRAC agreed to request the MAH for Vipidia and Trajenta to provide a cumulative review of all cases concerning arthralgia, both from clinical trials and spontaneous cases reported with linagliptin or alogliptin containing products.

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

#### **Summary of recommendation(s)**

- The MAHs for Vipidia (alogliptin) and for Trajenta (linagliptin) should submit to the EMA, within 60 days, a cumulative review of all cases concerning arthralgia, both from clinical trials and spontaneous cases reported with linagliptin- or alogliptin-containing products. With this cumulative review, the MAHs should provide a discussion regarding a potential class effect and also discuss relevant non-clinical data and scientific literature. Based on the outcome of the review, the MAHs should discuss the need for an update of the product information and/or the risk management plan as applicable. If the MAHs consider that this adverse drug reaction is not applicable for their respective medicinal product, a scientific rationale should be provided as to why their product would differ from the others in the class in this respect.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### **4.3. Signals follow-up and prioritisation**

#### **4.3.1. Adalimumab – HUMIRA (CAP) – EMEA/H/C/00000481/SDA/0242**

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Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of convulsion  
EPITT 18211 – Follow-up to July 2015

#### **Background**

For background information, see [PRAC minutes March 2015](#) and [PRAC minutes July 2015](#). The MAH replied to the request for information on the signal of convulsion and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC discussed the MAH's responses. Taking into account the available data from post-marketing, clinical trials and the literature included in the cumulative review provided by the MAH for Humira, the PRAC concluded that there is insufficient evidence of an association between adalimumab and convulsion and therefore no further actions are deemed necessary at this time.

#### **Summary of recommendation(s)**

- No regulatory action was considered necessary based on this signal.

#### 4.3.2. Anakinra - KINERET (CAP) - EMEA/H/C/000363/SDA/026

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of thrombocytopenia  
EPITT 18337 – Follow-up to June 2015

##### **Background**

For background information, see [PRAC minutes June 2015](#). The MAH replied to the request for information on the signal of thrombocytopenia and the responses were assessed by the Rapporteur.

##### **Discussion**

The PRAC discussed the cumulative review of cases of thrombocytopenia in association with anakinra. Taking into account the available evidence from EudraVigilance and the literature, the data submitted by the MAH as well as a plausible mechanism associated with the inhibition of interleukin 1 $\beta$  (IL-1 $\beta$ ) by anakinra, the PRAC agreed that the product information should be updated to include thrombocytopenia as a new undesirable effect.

##### **Summary of recommendation(s)**

- The MAH for Kineret (anakinra) should submit to the EMA, within 60 days, a variation to include thrombocytopenia as a new undesirable effect.

For the full PRAC recommendations, see [EMA/PRAC/661789/2015](#) published on 03/11/2015 on the EMA website.

#### 4.3.3. Boceprevir – VICTRELIS (CAP) - EMEA/H/C/002332/SDA/037

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Isabelle Robine

Scope: Signal of hyponatraemia  
EPITT 18350 – Follow-up to June 2015

##### **Background**

For background information, see [PRAC minutes June 2015](#). The MAH replied to the request for information on the signal of hyponatraemia and the responses were assessed by the Rapporteur.

##### **Discussion**

The PRAC discussed the cumulative review of cases of hyponatraemia in association with boceprevir. Taking into account the limited evidence provided by these cases as well as the absence of a plausible mechanism for boceprevir-induced hyponatraemia, the PRAC agreed that no changes to the product information are warranted for the time being but that the MAH for Victrelis should continue to monitor the event of hyponatraemia in forthcoming PSURs and provide an updated safety review, should additional relevant cases be received.

##### **Summary of recommendation(s)**

- The MAH for Victrelis (boceprevir) should continue to monitor cases of hyponatraemia and provide an updated safety review in the next PSUR if additional relevant cases are reported.

#### 4.3.4. Fluoroquinolones: Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

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Applicant: Bayer, Sanofi, various

PRAC Rapporteur: Valerie Strassmann

Scope: Signal of retinal detachment  
EPITT 15914 – Follow-up to June 2015

##### **Background**

For background information, see [PRAC minutes April 2013](#), [PRAC minutes June 2014](#) and [PRAC minutes June 2015](#). The authors of the recent French Agency (ANSM) study submitted answers to the list of questions adopted by the PRAC in June 2015. In addition, the MAHs for fluoroquinolone-containing medicinal products for systemic use submitted a cumulative review of cases of retinal detachment, retinal scar, retinal tear, chorioretinal scar, and retinoschisis in association with systemic fluoroquinolone intake. All these responses were assessed by the Rapporteur.

##### **Discussion**

The PRAC discussed the answers submitted by the authors of the ANSM study and agreed that some outstanding issues should be clarified before it can be concluded whether updates of the product information of fluoroquinolone-containing medicinal products are necessary. Therefore the PRAC agreed that the study authors should be requested to provide answers to a further list of questions. The PRAC also discussed the assessment of the MAHs' cumulative reviews of case reports. In total 10 new, formerly unknown cases have been retrieved by the search in the MAHs' global databases. For 4 of these 10 cases causality was assessed at least as possible and the overall number of cases with at least possible causality totals 15. However, the PRAC noted that the overall number of case reports is small compared to the large exposure with systemic fluoroquinolones, and a reporting bias cannot be excluded.

##### **Summary of recommendation(s)**

- The authors of the recent ANSM study should be requested to provide answers, within 90 days, to a further list of questions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.3.5. Mitotane – LYSODREN (CAP) – EMEA/H/C/000521/SDA/023

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Applicant: Laboratoire HRA Pharma, SA

PRAC Rapporteur: Dolores Montero Corominas



Scope: Signal of sex hormone disturbances and development of ovarian macrocysts  
EPITT 18301 – Follow-up to May 2015

### **Background**

For background information, see [PRAC minutes May 2015](#). The MAH replied to the request for information on the signal of sex hormone disturbances and development of ovarian macrocysts and the responses were assessed by the Rapporteur.

### **Discussion**

The PRAC discussed the MAH's responses. The MAH retrieved four publications leading to identification of 3 reported cases from the scientific literature and also presented the results of a search in the Medical Dictionary for Regulatory Activities (MedDRA) related to the effect of mitotane on development of ovarian cysts. However, the MAH did not provide a comprehensive review of the effect of mitotane on sex hormone metabolism in scientific literature as requested by the PRAC in May 2015. In addition, within the information provided by the MAH, there is no evidence that a search for case reports regarding the effect of mitotane on sex hormone metabolism has been carried out either. As part of its responses, the MAH also proposed to amend the product information. The PRAC agreed that an update of the product information is warranted but requested the MAH to provide additional information before concluding on the nature of the product information update.

### **Summary of recommendation(s)**

- The MAH for Lysodren (mitotane) should submit to the EMA, within 60 days, responses to a list of questions.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.6. [Sitagliptin - JANUVIA \(CAP\) - EMEA/H/C/000722/SDA/036, RISTABEN \(CAP\) - EMEA/H/C/001234/SDA/014, TESAVEL \(CAP\) - EMEA/H/C/000910/SDA/030, XELEVIA \(CAP\) - EMEA/H/C/000762/SDA/035](#)  
[Sitagliptin, metformin – EFFICIB \(CAP\) - EMEA/H/C/000896/SDA/017, JANUMET \(CAP\) - EMEA/H/C/000861/SDA/017, RISTFOR \(CAP\) - EMEA/H/C/001235/SDA/013, VELMETIA \(CAP\) - EMEA/H/C/000862/SDA/017](#)

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Signal of intestinal obstruction  
EPITT 18251 – Follow-up to April 2015

### **Background**

For background information, see [PRAC minutes April 2015](#). The MAHs replied to the request for information on the signal of intestinal obstruction and the responses were assessed by the Rapporteur.

### **Discussion**

The PRAC discussed the MAH's responses. The non-clinical data showed that sitagliptin does not acutely affect gastrointestinal motility and does not lead to gastrointestinal

stenosis/obstruction or gastrointestinal lesions. Available data from clinical trials did not show evidence for this risk. With regard to the spontaneous reports, the majority of cases either lacked sufficient information or presented confounding factors (e.g. pre-existing/concurrent conditions or concomitant medications). Overall, data from non-clinical studies, clinical trials and post-marketing experience did not support a causal relationship between gastrointestinal stenosis/obstruction and sitagliptin. Taking into account the available evidence, the PRAC agreed that there is currently insufficient evidence to establish a causal relationship between gastrointestinal stenosis/obstruction and sitagliptin. Therefore no changes to the product information are warranted but it was recommended that the MAH for Januvia (sitagliptin) should continue to monitor events of intestinal obstruction as part of routine safety surveillance.

#### **Summary of recommendation(s)**

- The MAH for Januvia (sitagliptin) should continue to monitor events of intestinal obstruction as part of routine safety surveillance and new relevant cases of gastrointestinal stenosis/obstruction should be presented and assessed in future PSURs.

## **5. Risk management plans (RMPs)**

### **5.1. Medicines in the pre-authorisation phase**

The PRAC provided advice to the CHMP on the proposed RMPs for a number of 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 14.1.

#### **5.1.1. Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) - EMEA/H/C/003982**

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Scope: Vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib)

#### **5.1.2. Lesinurad - EMEA/H/C/003932**

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Scope: Treatment of hyperuricaemia

#### **5.1.3. Migalastat - EMEA/H/C/004059, Orphan**

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Applicant: Amicus Therapeutics UK Ltd

Scope: Treatment of patients with Fabry disease

#### 5.1.4. Osimertinib - EMEA/H/C/004124

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Scope: Treatment of non-small-cell lung cancer (NSCLC)

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

None

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

See also Annex I 14.3.

#### 5.3.1. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/II/0037

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information to include additional warning and guidance on progressive multifocal leukoencephalopathy (PML). The Package Leaflet is updated accordingly

#### **Background**

Fingolimod is a sphingosine 1-phosphate receptor modulator indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions.

The CHMP is evaluating a type II variation procedure for Gilenya, a centrally authorised product containing fingolimod, to update the safety information to include additional warnings and guidance on the risk of progressive multifocal leukoencephalopathy (PML). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation.

#### **Summary of advice**

- The RMP version 11.0 for Gilenya (fingolimod) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The PRAC considered that a direct healthcare professional communication (DHPC) was necessary in order to communicate to HCPs on the potential risks related to the immunosuppressive effect of fingolimod, such as opportunistic infections and skin cancer. The PRAC agreed the content of the DHPC.

#### 5.3.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/II/0079

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Extension of indication to add the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 are updated. The Package Leaflet and RMP (version 25.0) are updated accordingly

## Background

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

The CHMP is evaluating an extension of the therapeutic indication for Revlimid, a centrally authorised product containing lenalidomide, to include the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes March 2015](#) and [PRAC minutes July 2015](#).

## Summary of advice

- The RMP version 27.0 for Revlimid (lenalidomide) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses are received to a request for supplementary information.
- The PRAC considered that the RMP should be updated to include the outcome in patients with high tumour burden as an important potential risk. In addition, the PRAC was concerned about the feasibility of the PASS on RRMCL as proposed by the MAH due to the inherent limitations of the proposed healthcare and pharmacy databases as well as cancer registries to yield reliable information on lenalidomide exposure. The MAH should further explore the possibilities for undertaking a PASS. Furthermore, the MAH should also propose alternative data collection (e.g. via a targeted questionnaire) and provide assessment of these data in the next PSUR.

### 5.3.3. Thalidomide – THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0043

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Update of sections 4.2 and 4.8 of the SmPC in order to add new dosing information for elderly patients (>75 years) with untreated multiple myeloma receiving thalidomide in combination with melphalan and prednisone (MPT). In addition, the MAH is updating the posology with the recommended starting doses for melphalan and prednisone for completeness. The Package Leaflet is updated accordingly

## Background

Thalidomide is an immunosuppressant indicated in combination with melphalan and prednisone as a first line treatment of patients with untreated multiple myeloma, aged 65 years and over or ineligible for high dose chemotherapy.

The CHMP is evaluating a type II variation procedure for Thalidomide Celgene, a centrally authorised product containing thalidomide, to include new dosing information for elderly

patients (above 75 years) with untreated multiple myeloma receiving thalidomide in combination with melphalan and prednisone (MPT) and to update the posology with the recommended starting doses for melphalan and prednisone. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes June 2015](#).

#### **Summary of advice**

- The RMP version 17.0 for Thalidomide Celgene (thalidomide) in the context of the variation under evaluation by the CHMP was acceptable.
- The PRAC reviewed and agreed the proposed DHPC aimed at communicating the recommendation to reduce the starting dose of thalidomide when combined with melphalan in patients over 75 years.

## **6. Periodic safety update reports (PSURs)**

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

See also Annex I 15.1.

#### **6.1.1. Canagliflozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP) - PSUSA/10077/201503**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Invokana and Vokanamet, centrally authorised medicines containing canagliflozin and canagliflozin/metformin respectively, and issued a recommendation on their marketing authorisations.

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Invokana (canagliflozin) and Vokanamet (canagliflozin/metformin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add renal failure occurring mainly in association with volume depletion as a new undesirable effect with an

uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>4</sup>.

- In the next PSUR, the MAH should evaluate all cases of renal cell cancer with regard to preceding (recurrent) urinary tract infections. The MAH should provide a cumulative review of cases of pulmonary embolism and pancreatitis. In addition, the MAH should state whether the narratives of fungal infection cases were evaluated in order to detect additional cases of urogenital infections. The MAH should also compare rate and pattern of cases concerning elderly patients with those of younger patients and provide such comparison. Furthermore, the MAH should review the interaction with lithium and consider updating the product information accordingly as applicable. Finally, the MAH should provide a cumulative review of cases of Steven-Johnsons-syndrome/bullous efflorescence of hypersensitivity origin in the PSUR after the next one.
- The MAH should be requested to amend the RMP at the next regulatory procedure affecting the RMP or within the next PSUR to change renal failure from an important potential to an important identified risk and to consider including hypersensitivity reactions (including rash, urticaria and angioedema) as an important identified risk.

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. Colesevelam – CHOLESTAGEL (CAP) - PSUSA/00864/201503

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Colesevelam is a lipid-lowering polymer indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels as well as for the reduction of elevated total-cholesterol and LDL-C in adult patients under certain conditions. Colesevelam is also indicated in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Cholestagel (colesevelam) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.

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<sup>4</sup> 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 discuss serious and non-serious cases of myalgia with the aim to further characterize the risk in terms of risk factors or at risk populations. The MAH should also discuss the cases of rhabdomyolysis. Finally, the MAH should closely monitor cardiac and cerebrovascular accident (CVA) events.
- The MAH should submit to EMA, within 6 months, proposals to improve the ease of administration of Chloestagel, due to the increased number of cases reporting 'drug administration error' compared to the previous PSUR, in particular cases where tablets were either crushed or cut.

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. Dimethyl fumarate – TECFIDERA (CAP) - PSUSA/10143/201503

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **Background**

Dimethyl fumarate is a methyl ester of fumaric acid indicated for the treatment of adult patients with relapsing remitting multiple sclerosis.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Tecfidera (dimethyl fumarate) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should closely monitor reported cases with dyspnoea and relevant events. In addition, the MAH should discuss a potential but currently theoretical pharmacodynamic mechanism relating to adverse events reported with new onset diabetes. The MAH should also provide a brief description, including a brief causality assessment of all relevant cases of new onset diabetes, hyperglycaemia, convulsion, renal failure and relevant cases with signs and symptoms of Fanconi syndrome.
- The MAH should submit to the EMA, within 60 days, via the appropriate regulatory procedure the results of study P00012-14-02 (study number: WIL-793019): *an oral gavage) toxicity study of dimethyl fumarate in juvenile rats*, with a thorough discussion of the results.

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

#### 6.1.4. Enfuvirtide – FUZEON (CAP) - PSUSA/01217/201503

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Applicant: Roche Registration Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

##### **Background**

Enfuvirtide is a fusion inhibitor indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV)-1 infected patients under certain conditions.

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

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Fuzeon (enfuvirtide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add that enfuvirtide may be associated with cutaneous amyloidosis at the injection site in the undesirable effects section under 'description of selected adverse reactions'. Therefore the current terms of the marketing authorisation(s) should be varied<sup>5</sup>.
- In the next PSUR, the MAH should continue to closely monitor cases of cutaneous amyloidosis at the injection site as well as cases of systemic amyloidosis.

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. Everolimus – AFINITOR (CAP) - PSUSA/10268/201503

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor indicated for the treatment of hormone receptor-positive HER2/neu negative advanced breast cancer, unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin as well as for the treatment of advanced renal cell carcinoma under certain conditions.

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<sup>5</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion



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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Afinitor (everolimus) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a detailed analysis comparing safety data of pre-treated versus non pre-treated patients regarding the missing information 'pre-treatment with cytotoxic therapies before everolimus treatment'. Regarding missing information, the MAH should provide an analysis comparing safety data of everolimus monotherapy with safety data when everolimus is used in combination with exemestane. In addition, the MAH should provide the pooled number of patients receiving placebo in the pooled safety data set and explain the 10% threshold. The MAH should clarify why the difference in incidence compared to placebo is shown to be non-significant (difference  $\leq 10\%$ ) across all studies in the pooled safety data set.
- The MAH should submit to EMA, within 60 days, a cumulative review of all cases of ejection fraction decreased with a detailed analysis of the discrepancies in the number of cases reported in this PSUR and the previous one. The MAH should also provide frequencies of ejection fraction decreased of all studies in authorised indications comparing everolimus with placebo. In addition, the MAH should update its causality analysis with recommendations, missing cases and further consider whether an update of the product information is warranted.

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.

In light of the available data on everolimus indicated in transplant settings with regard to lymphoedema, the PRAC agreed to request relevant MAHs to submit, within 60 days, to the national competent authorities all supportive evidence together with a proposal for an update of the product information (section 4.8 of the SmPC and package leaflet) through the appropriate variation application. The MAHs should consider whether further amendments of the product information are warranted.

#### **6.1.6. Exenatide – BYDUREON (CAP), BYETTA (CAP) - PSUSA/09147/201503**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### **Background**

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination for the treatment of type 2 diabetes mellitus under certain conditions. Exenatide is also

indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone under certain conditions.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bydureon and Byetta (exenatide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to amend the frequency of some undesirable effects based on the update of the MAH's safety database with additional clinical trials completed since the granting of the marketing authorisation. In addition, the frequency of the undesirable effects pancreatitis and interaction with warfarin was changed to unknown based on post-marketing data only. Therefore the current terms of the marketing authorisation(s) should be varied<sup>6</sup>.
- In the next PSUR, the MAH should monitor cases of serious bullous conditions/skin reactions, including toxic epidermal necrolysis, serious injection site reactions, as well as reporting rate for pancreatitis, pancreatic cancer and thyroid cancer. The MAH should present the reports on serious injection site reactions separately for the single dose tray (SDT) and dual chamber pen (DCP) presentations for exenatide once weekly (QW) together with exposure data presented separately for the SDT and DCP presentations.

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

#### **6.1.7. Ipilimumab – YERVOY (CAP) - PSUSA/09200/201503**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

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

#### **Summary of recommendation(s) and conclusions**

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<sup>6</sup> Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Yervoy (ipilimumab) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a new warning that cases of 'Vogt-Koyanagi-Harada syndrome' have been reported post-marketing and to add 'Vogt-Koyanagi-Harada syndrome' as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>7</sup>.
- In the next PSUR, the MAH should provide information on cases of autoimmune disease reactivation/aggression in those with a history of these conditions. The MAH should also provide a review of the potential risk of ipilimumab predisposing patients to hypersensitivity skin drug reactions. Finally the MAH should closely monitor venous thromboembolism cases.

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

### 6.1.8. Regorafenib – STIVARGA (CAP) - PSUSA/10133/201503

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **Background**

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

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Stivarga (regorafenib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include in the undesirable effects section clinically relevant information on severe liver injury, including the observed time to onset (within first 2 months) and the hepatocellular pattern of liver injury and to include that a higher incidence of fatal liver injury in Japanese patients compared to non-Japanese patients treated with regorafenib has been observed. Therefore the current terms of the marketing authorisation(s) should be varied<sup>8</sup>.

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<sup>7</sup> 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

<sup>8</sup> 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 closely monitor drug reaction with eosinophilia and systemic symptoms (DRESS) and discuss all available data. If appropriate the MAH should propose amendments to the SmPC. The MAH should further monitor the signal of haemolytic anaemia and (acute) pancreatitis. The MAH should provide an updated causality assessment for the cases for which discrepancies were noted between the PRAC's assessment and the assessment done the MAH.

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. Tacrolimus – PROTOPIC (CAP) - PSUSA/02840/201503

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### **Background**

Tacrolimus is an inhibitor of calcium-dependent signal T cells transduction pathways and is indicated for the treatment of moderate to severe atopic dermatitis under certain conditions.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Protopic (tacrolimus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add ophthalmic herpes infection as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>9</sup>.
- In the next PSUR, the MAH should keep the signal of non-cutaneous infections as on-going. The MAH should provide a critical analysis, not just focussing on the numbers of cases reported, including a clinical evaluation of the interval data. The MAH should continually monitor non-specialist use, including data from additional sources and provide an analysis of this issue. The MAH should discuss the time to onset between first application of Protopic and reported cases of malignancy, utilising details of data reported, including those received from the lymphoma questionnaire. Finally the MAH should provide a review of pancreatitis in association with topical tacrolimus, including all relevant data, non-clinical, clinical and literature.

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.

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<sup>9</sup> 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

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **Background**

Teriflunomide is an immunomodulatory agent indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

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

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Aubagio (teriflunomide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to amend the current warning on skin reactions to reflect that Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported post-marketing, to add severe skin reactions, hypersensitivity reactions (immediate or delayed) including anaphylaxis and angioedema, and severe infections including sepsis as new undesirable effects with an unknown frequency, to add creatinine phosphokinase (CPK) increase, arthralgia and palpitations as new undesirable effects with a common frequency, to add headache as a new undesirable effect with a very common frequency. In addition the undesirable effects section has been extensively revised in particular to update the frequencies of the undesirable effects. Therefore the current terms of the marketing authorisation(s) should be varied<sup>10</sup>.
- In the next PSUR, the MAH should further closely monitor the risk of interstitial lung disease and should reflect this risk adequately in the RMP. The MAH should further closely monitor the risk of new onset diabetes/hyperglycaemia/diabetes, provide a full analysis of the available evidence and should discuss whether diabetes mellitus/hyperglycaemia should be included in the product information. The MAH should discuss all events of hyperglycaemia and corresponding events from non-interventional studies and other sources as already recommended from the last PSUR. The MAH should also discuss cases of carpal tunnel syndrome, cases with regard to expectedness and should perform a detailed review on the potential mechanism of action. From the previous PSUR, the PRAC noted a number of reports of adverse reactions, which are not labelled in the current SmPC for teriflunomide, but are stated in the SmPC of the parent compound leflunomide, Hence, the MAH should discuss all potential implications regarding safety aspects for teriflunomide on relevant topics available for leflunomide within upcoming PSURs.

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<sup>10</sup> 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

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

#### 6.1.11. Vildagliptin - GALVUS (CAP), JALRA (CAP), XILIRX (CAP); metformin, vildagliptin – EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP) - PSUSA/03113/201502

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### **Background**

Vildagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment of type 2 diabetes mellitus in adults under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Galvus, Jalra, Xiliarx as well as Eucreas, Icandra and Zomarist, centrally authorised medicines containing vildagliptin and vildagliptin/metformin respectively, and issued a recommendation on their marketing authorisations.

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Galvus, Jalra, Xiliarx (vildagliptin) as well as Eucreas, Icandra and Zomarist (vildagliptin/metformin) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the drug-drug interaction between angiotensin-converting-enzyme (ACE) inhibitors and vildagliptin resulting in an increased risk of angioedema. Therefore the current terms of the marketing authorisation(s) should be varied<sup>11</sup>.
- In the next PSUR, the MAH should provide another review of all cases of intestinal obstruction/stenosis. The MAH proposed to remove breast cancer and neuropsychiatric events (depression) as important potential risks in the RMP. The MAH should justify this proposal by providing the full case narratives, including analysis and discussion.
- The MAH should submit to the EMA, within 30 days, all HCP narratives for renal failure cases with vildagliptin (Galvus/Eucreas). The MAH should also provide a tabulation containing the case ID, time to onset, medical history and other suspected drugs as well as a causality assessment. Cases with renal failure potentially caused by dehydration should be highlighted.

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<sup>11</sup> Update of SmPC section 4.5. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

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

See also Annex I 15.2.

### **6.2.1. Voriconazole – VFEND (CAP), NAP - PSUSA/03127/201502**

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Applicant: Pfizer Limited, various

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **Background**

Vfend is a triazole antifungal agent used in the treatment under certain conditions of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections, serious fungal infections caused by *Scedosporium* and *Fusarium* and prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant recipients.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of voriconazole-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information should be updated to clarify the photosensitivity reactions observed with voriconazole and to add ephelides and lentigo as new undesirable effects with an unknown frequency as well as actinic keratosis with a rare frequency. Therefore the current terms of the marketing authorisations should be varied<sup>12</sup>.

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

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

See also Annex I 15.3.

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<sup>12</sup> 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

Applicant: various

PRAC Lead: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure

#### **Background**

Amitriptyline is a tricyclic antidepressant with potent anticholinergic, antihistaminergic and sedative properties which potentiates the effects of catecholamines. It is indicated for the treatment of depression under certain conditions, and nocturnal enuresis where organic pathology is excluded, and when non-drug therapy and first line pharmacotherapy has failed, and chronic pain (central or peripheral neuropathic pain, fibromyalgia), as an adjunct under certain conditions.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of amitriptyline-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning highlighting that amitriptyline has been found to cause prolongation of the QT interval and arrhythmia and to add electrocardiogram QT prolonged as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>13</sup>.
- In the next PSUR, the MAH(s) should address the following safety concerns as important risks: suicidality, hyponatremia, Brugada syndrome, serotonin syndrome, QT prolongation and Torsades de Pointes, disturbances in consciousness (somnolence, sedation, syncope, coma, coma scale abnormal), cardiac arrest and cardio-respiratory arrest, respiratory arrest with amitriptyline overdose, use in pregnancy and lactation, death (including unexpected death, sudden death, accidental death), overdose, use in patients with pheochromocytoma, porphyria; as important potential risks: schizophrenia, psychosis, hallucinations, paranoid delusions, hostility/aggression and self injurious ideation in children and adolescents, nystagmus, haemodynamic instability (including circulatory collapse); and as missing information: thyroid adenoma, encephalopathy, congenital, familial and genetic disorders, paediatric and adolescent use, lack of therapeutic efficacy, off-label use.

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

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<sup>13</sup> 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



### 6.3.2. Amitriptyline, perphenazine (NAP) - PSUSA/00170/201501

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Applicant: various

PRAC Lead: Leonidas Klironomos

Scope: Evaluation of a PSUSA procedure

#### **Background**

Amitriptyline is a tricyclic antidepressant with potent anticholinergic, antihistaminergic and sedative properties which potentiates the effects of catecholamines. Perphenazine is a piperazine derivative of phenothiazide possessing antipsychotic activity most likely secondary to its ability to block the dopamine receptor 2 receptors. The combination amitriptyline/perphenazine is indicated for the treatment of depression associated with anxiety under certain conditions.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of amitriptyline/perphenazine-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning highlighting that amitriptyline as monocomponent has been found to cause prolongation of the QT interval and arrhythmia and to add electrocardiogram QT prolonged as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSUR, the MAH should address the following safety concerns as important risks: suicidality, hyponatremia, Brugada syndrome, cardiac failure, cardiac arrest (including cardio-respiratory arrest), respiratory arrest with amitriptyline overdose, use in pregnancy and lactation, death (including unexpected death, sudden death), overdose, QT prolongation; as important potential risks: dyspnoea, use in patients with pheochromocytoma; and as missing information: disseminated intravascular coagulation, coagulopathy, dementia, paediatric and adolescent use.

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

### 6.3.3. Ampicillin, sulbactam (NAP) - PSUSA/00000197/201502

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Applicant: various

PRAC Lead: Carmela Macchiarulo

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<sup>14</sup> 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

Scope: Evaluation of a PSUSA procedure

## Background

Ampicillin is an aminopenicillin with bactericidal properties that acts against sensitive organisms during the stage of active multiplication by inhibition of biosynthesis of cell wall mucopeptide. Sulbactam, a derivative of the basic penicillin nucleus, enhances the activity of penicillins and cephalosporins against many resistant strains of bacteria. The combination ampicillin/sulbactam is indicated for infections caused by susceptible microorganisms, including the treatment of upper and lower respiratory tract infections including sinusitis, otitis media, and epiglottitis, bacterial pneumonias, urinary tract infections and pyelonephritis, intra-abdominal infections including peritonitis, cholecystitis, endometritis, and pelvic cellulitis, bacterial septicemia, skin, soft tissue, bone and joint infections, gonococcal infections.

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

## Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of ampicillin/sulbactam-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning that drug induced liver injury including cholestatic hepatitis with jaundice has been associated with the use of ampicillin/sulbactam and to add angioedema, erythema and urticaria as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>15</sup>.
- In the next PSUR, the MAH should closely monitor events and provide cumulative reviews for disseminated intravascular coagulation, cardiac injury, drug ineffective/lack of efficacy, rhabdomyolysis, renal injury, linear immunoglobulin A (IgA) disease, interstitial lung disease, hepatic disorders, resistance to ampicillin/sulbactam, dyspnoea. In addition, effects on renal, hepatic and hematopoietic system following long term administration of ampicillin/sulbactam and serious skin reactions should be considered as important potential risks.

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. Argatroban (NAP) - PSUSA/00009057/201501

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Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

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<sup>15</sup> 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

## Background

Argatroban is a synthetic, direct, and selective thrombin inhibitor and exerts its anticoagulant effects by inhibiting thrombin-catalysed or induced reactions, including fibrin formation, activation of some coagulation factors, protein C, and platelet aggregation. It is indicated for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) type II.

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

## Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of argatroban-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add cerebral haemorrhage as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.
- The MAHs which have an RMP in place should amend the risk of cerebral haemorrhage from an important potential to an important identified risk in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.

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

### 6.3.5. Cilostazol (NAP) - PSUSA/00010209/201502

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Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

## Background

Cilostazol is a dihydro-quinolinone derivative that inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase, suppressing cAMP degradation and thereby increasing cAMP levels in platelets and blood vessels. It is indicated for the improvement of the maximal and pain-free walking distances in patients with intermittent claudication (IC), who do not have rest pain and who do not have evidence of peripheral tissue necrosis. It is for second-line use in patients in whom lifestyle modifications (including smoking cessation and exercise programmes) and other appropriate interventions have failed to sufficiently improve their IC symptoms.

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<sup>16</sup> 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

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of cilostazol-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the findings from non-clinical studies in mice which show that include that cilostazol reversibly impaired fertility of female mice but not in other animal species in the fertility, pregnancy and lactation section of the SmPC. In addition the preclinical section of the SmPC was updated to reflect the findings of these studies. The clinical significance of these findings is unknown. Therefore the current terms of the marketing authorisation(s) should be varied<sup>17</sup>.
- In the next PSUR, the innovator MAH should provide a cumulative review of a number of adverse events based on information from clinical trials, spontaneous reports, and published literature, with a focus on whether there is sufficient evidence to update the product information. In addition, the innovator MAH should provide further details relating to study 021-KOA-1201n.

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

#### **6.3.6. Clobetasol (NAP) - PSUSA/00000799/201502**

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Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

#### **Background**

Clobetasol is a potent topical corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of steroid-responsive dermatoses that are resistant to less potent corticosteroids. In addition, clobetasol is indicated for the treatment of moderate to severe forms of psoriasis, lichen planus, discoid lupus erythematosus, recalcitrant dermatoses and other skin conditions that do not respond satisfactorily to less potent corticosteroids.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of clobetasol-containing products in the approved indication(s) remains favourable.

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<sup>17</sup> Update of SmPC sections 4.6 and 5.3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should consider the following safety concerns as new safety signals: necrotising fasciitis, diabetes mellitus/diabetes mellitus inadequate control, Kaposi's sarcoma and osteonecrosis. In addition, the MAHs should discuss specifically the following safety concerns: Cushing's syndrome and hypothalamic-pituitary adrenal axis suppression, eye disorders, including cataract and glaucoma, immunosuppression and opportunistic infections, growth retardation and serious skin disorders.

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. Nomegestrol (NAP) - PSUSA/00002181/201501

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Applicant: various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

#### **Background**

Nomegestrol is a progestogen structurally related to progesterone, indicated in the treatment of menstrual disorders in pre-menopausal women (premenstrual syndrome, oligomenorrhoea, primary dysmenorrhoea, mastodynia, polymenorrhoea, amenorrhoea, menorrhagia, menstrual cycle prolonged, genital bleeding), and as a hormone therapy in postmenopausal women.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of nomegestrol-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAHs which have an RMP in place should include the risk of meningioma as an important potential risk in the next RMP update within an upcoming regulatory procedure affecting the RMP.

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. Ondansetron (NAP) - PSUSA/00002217/201502

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Applicant: various

PRAC Lead: Milena Radoha-Bergoč

Scope: Evaluation of a PSUSA procedure

## Background

Ondansetron is a serotonin 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonist indicated in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (CINV/RINV), the management of post-operative nausea and vomiting (PONV). In the paediatric population, ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged  $\geq 6$  months and for the prevention and treatment of PONV in children aged  $\geq 1$  month.

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

## Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of ondansetron-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include information on accidental overdose of ondansetron leading to serotonin syndrome in the paediatric population. Therefore the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the innovator MAH should discuss the increase in the overall number of reported adverse drug reactions. The MAH should also provide a thorough discussion (including analysis, demographic and special population data, and evaluation of the increase of off-label use) based on the 54 new cases of off-label use. Congenital cardiac septal defect should be also closely monitored.
- In the next PSUR, the MAHs should closely monitor events of renal failure, intestinal obstruction, lack of efficacy with concurrent serotonergic antidepressants and provide cumulative reviews. The MAHs should also discuss use in pregnancy (analysis of reports and conclusions, literature data; including pregnancy outcome of anencephaly and congenital malformations) and provide a cumulative review.
- In addition, given the potential risk of the off-label use of ondansetron during pregnancy and the seriousness of the issue, the PRAC agreed on the need to submit the results of the evaluation of congenital cardiac septal defects, including a detailed discussion based on a cumulative review and the available evidence as soon as possible and no later than 3 months to the national competent authorities.

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. Potassium para aminobenzoate (NAP) - PSUSA/00010130/201502

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Applicant: various

<sup>18</sup> Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **Background**

Potassium para aminobenzoate belongs to the pharmacotherapeutic group of antifibrosis agents and is indicated in adult patients for the treatment of scleroderma and for the reduction of progression of penile curvature in active Induratio penis plastica (IPP/Peyronie's disease).

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

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of potassium para aminobenzoate-containing products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should review and discuss cumulative data possibly indicating hypersensitivity reactions (including skin, hepatobiliary and pulmonary reactions). Taking into consideration the information provided in the product information, hypersensitivity reactions should also be defined as an important identified risk. In addition, the MAHs should provide a cumulative review of cardiac disorders. Possible consequences for the product information regarding the co-administration with other potassium-containing medicines or angiotensin II type 1 receptor blockers should be discussed.

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. Tenoxicam (NAP) - PSUSA/00002893/201502**

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

### **Background**

Tenoxicam is an anti-inflammatory drug substance belonging to the -oxicam class; it has anti-inflammatory, analgesic and antipyretic properties as well as thrombocytic antiaggregation activity. It is indicated for the symptomatic treatment of inflammatory and degenerative rheumatic diseases.

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

## Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of tenoxicam-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include the increased risk of the serious consequences of adverse reactions in the elderly and the need for nonsteroidal anti-inflammatory drugs (NSAIDs) dose and duration of treatment adjustment in this population. In addition the product information should be updated to add visual disturbances (such as visual impairment and vision blurred), confusional state, hallucinations, paraesthesia, somnolence as new undesirable effects with an unknown frequency and to add pancreatitis as a new undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAH should closely monitor cases of diplopia, systemic lupus erythematosus (SLE) and related symptoms such as optic neuritis and aseptic meningitis reported with tenoxicam. In view of the available data regarding tenoxicam, the MAHs should also discuss specifically safety concerns: as important identified risks gastrointestinal bleeding, ulceration or perforation, life-threatening cutaneous reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); as important potential risks arterial thrombotic events, cardiac disorder (palpitations, cardiac failure), renal disorder (effect of renal haemodynamics), hepatobiliary disorders (hepatitis); risk of masking of the usual sign of infections; and as missing information use in children and use in pregnancy and breastfeeding.
- The contra-indication 'last trimester of pregnancy' should be added as agreed by the CHMP Pharmacovigilance Working Party (PhVWP) in the tenoxicam-containing products that do not include this contra-indication in their respective product information (SmPC sections 4.3 and 4.6). This amendment can be handled via relevant national variation procedure(s) to be submitted within 60 days following this PRAC recommendation.

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

### 6.4.1. Tocilizumab – ROACTEMRA (CAP) - EMEA/H/C/000955/LEG/050

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Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: From PSUSA/00002980/201410: Review of all cases of melanoma in association with tocilizumab that have become available since marketing approval and comparison of the (cumulative) incidence of melanomas (separated for skin and ocular melanoma) with background rates of melanomas in the target population (rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA)/polyarticular juvenile idiopathic arthritis (pJIA))

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<sup>19</sup> Update of SmPC sections 4.2 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



## Background

Tocilizumab is an interleukin inhibitor indicated for the treatment of severe, active and progressive rheumatoid arthritis (RA), for the treatment of moderate to severe active RA, for the treatment of active systemic juvenile idiopathic arthritis (sJIA) as well as for the treatment of polyarticular juvenile idiopathic polyarthritis (pJIA) under certain conditions.

Following the evaluation of the most recently submitted PSURs for RoActemra (tocilizumab), the PRAC requested the MAH to submit further data (see [PRAC minutes May 2015](#)). The responses were assessed by the Rapporteur for further PRAC advice.

## Summary of advice/conclusion(s)

- In the next PSUR, the MAH should provide a refined review of incidence rate of melanoma and provide a detailed comparison of rate estimates for melanoma in association with tocilizumab from clinical trials and the post-marketing setting.

## 7. Post-authorisation safety studies (PASS)

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>20</sup>

See also Annex I 16.1.

#### 7.1.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/0020.1

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a revised PASS protocol for study CC-5013-MM-034: 'a lenalidomide product registry of previously untreated adult multiple myeloma patients who are not eligible for transplant'

## Background

Revlimid is a centrally authorised medicine containing lenalidomide. It is indicated for the treatment of adult patients with previously untreated multiple myeloma and is used in combination with dexamethasone for the treatment of multiple myeloma in adult patients under certain conditions and for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes under certain conditions.

A revised protocol for a PASS (product registry) of transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM) treated with lenalidomide to gather safety data on the use of lenalidomide in NDMM patients was submitted to the PRAC in accordance with the conditions to the marketing authorisation (s).

## Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal

<sup>20</sup> In accordance with Article 107n of Directive 2001/83/EC

product as the Committee considered that that the design of the study did not fulfil the study objectives. A number of concerns regarding the primary study objective, the research questions and objectives, and the need to provide comparative data to be used for a risk estimate of the cardiovascular events should be resolved before the final protocol is approved. The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>21</sup>**

See also Annex I 16.2.

### **7.2.1. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/006**

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Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study DSE-EDO-04-14-EU: non-interventional study on edoxaban treatment in routine clinical practice for patients with non valvular atrial fibrillation

#### **Background**

Lixiana is a centrally authorised medicine containing edoxaban, a highly selective, direct and reversible inhibitor of factor Xa indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf) under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

As part of the RMP for Lixiana, a centrally authorised medicine containing edoxaban, the MAH was required to conduct a PASS on edoxaban treatment in routine clinical practice for patients with non-valvular atrial fibrillation (ETNA-AF-Europe) (category 3). The aim was to collect real world safety data on bleeding events including intracranial haemorrhage, drug related adverse events such as liver adverse events, cardiovascular (CV) and all-cause mortality in AF patients treated with edoxaban up to 4 years. The MAH submitted a draft protocol for study DSE-EDO-04-14-EU which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

#### **Summary of advice**

- The study protocol for study DSE-EDO-04-14-EU could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 60 days.
- The PRAC identified a number of limitations with this draft study protocol. The MAH should therefore address how to achieve meaningful results without a comparator, whether other sources of data have been explored, and whether the objectives should focus on how the data will inform the PRAC's understanding of the risks. The MAH should also comment on the 'unscheduled visits' to HCPs included in the protocol as

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<sup>21</sup> 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

this could be considered to contradict the non-interventional principle of the study, whether the proposed follow-up times/questionnaires would be expected as usual standard of care across different countries. The MAH should comment on the relevance of outcomes relating to Health Economics and Outcome Research and on the relevance of the proposed questionnaires (relating to quality of life and satisfaction with treatment) on the safety profile of edoxaban. Finally, the MAH should explore other sources (e.g. healthcare databases) to obtain further information on relevant safety outcomes.

### 7.2.2. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/007

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Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study DSE-EDO-05-14-EU: non-interventional study on edoxaban treatment in routine clinical practice in patients with venous thromboembolism in Europe

#### **Background**

Lixiana is a centrally authorised medicine containing edoxaban, a highly selective, direct and reversible inhibitor of factor Xa indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf) under certain conditions and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

As part of the RMP for Lixiana, a centrally authorised medicine containing edoxaban, the MAH was required to conduct a PASS on Edoxaban treatment in routine clinical practice for patients with acute venous thromboembolism in Europe (ETNA-VTE-Europe) (category 3). The aim was to collect real world safety data on bleeding events, drug related adverse events such as liver adverse events and mortality (VTE-related and all-cause) in VTE patients treated with edoxaban. The MAH submitted a draft protocol for study DSE-EDO-05-14-EU which was assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

#### **Summary of advice**

- The study protocol for study DSE-EDO-05-14-EU could be acceptable provided an updated protocol and satisfactory responses to a list of questions agreed by the PRAC is submitted to the EMA within 60 days.
- The PRAC however identified a number of limitations with this draft study protocol. The MAH should therefore address how to achieve clinically meaningful results without a comparator, whether other sources of data have been explored, and ensure that the objectives focus on how the data will inform the PRAC's understanding of the risks. The MAH should also comment on the 'unscheduled visits' to HCPs included in the protocol as this could be considered to contradict the non-interventional principle of the study and therefore clarification is required as to whether the proposed follow-up times/questionnaires would be expected as usual standard of care across different countries. The MAH should comment on the relevance of outcomes relating to Health Economics and Outcome Research and on the relevance of the proposed questionnaires

(relating to quality of life and satisfaction with treatment) on the safety profile of edoxaban.

### 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>22</sup>

#### 7.3.1. Trimetazidine (NAP) - EMEA/H/N/PSR/0001

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Dolores Montero Corominas

Scope: Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophtalmological and/or ear, nose and throat (ENT) indications among general practitioners, ophtalmologists and ENT specialists

##### **Background**

Trimetazidine is a metabolic agent indicated as add-on therapy for the symptomatic treatment of adults with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

In line with the conclusions of a referral under Article 31 of Directive 2001/83/EC conducted by the CHMP in 2012 for trimetazidine-containing medicines ([EMEA/H/A-31/1305](#)), MAHs were required to conduct a post-authorisation safety study (drug utilisation study) to verify the compliance of prescribers with respect to the restricted indication following the referral. The MAH submitted a draft protocol for this study for assessment by the PRAC (see [PRAC minutes February 2014](#)). The MAH submitted the final study results for assessment by the PRAC.

##### **Conclusion**

- The PRAC appointed Dolores Montero Corominas as PRAC Rapporteur for the assessment of the final study results and agreed a timetable for this procedure.

#### 7.3.2. Trimetazidine (NAP) - EMEA/H/N/PSR/0002

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Applicant: Lupin, various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Survey DUS: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain. Database DUS: Trimetazidine Drug Utilization Study in European Countries using databases – analysis for France, Hungary, Romania and Spain

##### **Background**

Trimetazidine is a metabolic agent indicated as add-on therapy for the symptomatic treatment of adults with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

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<sup>22</sup> In accordance with Article 107p-q of Directive 2001/83/EC

In line with the conclusions of a referral under Article 31 of Directive 2001/83/EC conducted by the CHMP in 2012 for trimetazidine-containing medicines ([EMA/H/A-31/1305](#)), MAHs were required to conduct a post-authorisation safety study (drug utilisation study) to verify the compliance of prescribers with respect to the restricted indication following the referral. A consortium of MAHs submitted a draft protocol for this study for assessment by the PRAC (see [PRAC minutes February 2014](#)). The consortium now submitted the final study results for assessment by the PRAC.

### Conclusion

- The PRAC appointed Dolores Montero Corominas as PRAC Rapporteur for the assessment of the final study results and agreed a timetable for this procedure.

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>23</sup>

See also Annex I 16.4.

- 7.4.1. [Pioglitazone – ACTOS \(CAP\) - EMA/H/C/000285/WS/0827](#); [GLUSTIN \(CAP\) - EMA/H/C/000286/WS/0827](#)  
[pioglitazone, glimepiride – TANDEMACT \(CAP\) - EMA/H/C/000680/WS/0827](#)  
[pioglitazone, metformin – COMPETACT \(CAP\) - EMA/H/C/000655/WS/0827](#);  
[GLUBRAVA \(CAP\) - EMA/H/C/000893/WS/0827](#)
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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: Submission of final results from observational study PROactive together with post-hoc analysis of Kaiser Permanente Northern California (KPNC) and comprehensive review of the data on prostate cancer risk. The RMP is updated accordingly

### Background

Actos and Glustin are centrally authorised medicines containing pioglitazone, a thiazolidinedione (TZD) with hypoglycemic (antihyperglycemic, antidiabetic) action indicated as second or third line treatment of type 2 diabetes mellitus as monotherapy, dual therapy or triple oral therapy under certain conditions. Tandemact is a centrally authorised medicine containing pioglitazone and glimepiride, a TZD and a sulfonylurea respectively, indicated as second line treatment of adult patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride. Competact and Glubrava are centrally authorised medicines containing pioglitazone and metformin, a TZD and a biguanide respectively, indicated as second line treatment of type 2 diabetes mellitus adult patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

The MAH had committed to perform the following non-interventional PASS: the PROactive extension study, an observational study of patient cohorts who previously received long-term treatment with pioglitazone or placebo in addition to existing antidiabetic medications

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<sup>23</sup> 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

(study AD-4833-EC445), as listed in the RMP. In addition the MAH also committed to perform post-hoc analyses of the Kaiser Permanente North Carolina (KPNC) non-bladder cancer malignancy study: a pharmacoepidemiological study using the KPNC database to explore the risk of other (non-bladder) neoplasia based on comparative incidence of non-bladder malignancy in type 2 diabetes I pioglitazone and non-pioglitazone users (study AD4833-403), as listed in the RMP. The Rapporteur assessed the final results from studies study AD-4833-EC445 and AD4833-403, as well as the requested cumulative review of the data from all relevant data sources in relation to prostate cancer.

#### **Summary of advice**

- The PRAC discussed the final results from the PROactive extension study, the post-hoc analyses of the Kaiser Permanente North Carolina (KPNC) non-bladder cancer malignancy study, to further explore the risk of prostate cancer, the cumulative review of the data from all relevant data sources in relation to prostate cancer and the RMP updates (Actos/Glustin version 22 and Competact/Glubrava version 20), submitted as type II variation EMEA/H/C/WS0827. In view of the review of the findings on prostate cancer, the PRAC agreed on a list of questions to the MAH to facilitate further characterisation of these observations in the context of its known safety profile.

### **7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>24</sup>**

See Annex I 16.5.

### **7.6. Others**

See Annex I 16.6.

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

### **8.1. Annual reassessments of the marketing authorisation**

See Annex I 17.1.

### **8.2. Conditional renewals of the marketing authorisation**

See also Annex I 17.2.

#### **8.2.1. Vandetanib – CAPRELSA (CAP) - EMEA/H/C/0002315/R/0015 (without RMP)**

Applicant: AstraZeneca AB

PRAC Rapporteur: Corinne Fechant

Scope: Conditional renewal of the marketing authorisation

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<sup>24</sup> In line with the revised variations regulation for any submission before 4 August 2013

## Background

Vandetanib is a protein kinase inhibitor indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Caprelsa, a centrally authorised product containing vandetanib, was authorised under conditional marketing authorisation in 2012. The PRAC is responsible for providing advice to the CHMP on this ongoing conditional renewal procedure with regard to specific obligations, safety and risk management related-aspects.

## Summary of advice

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, the PRAC considered that the conditional renewal procedure for Caprelsa (vandetanib) could be finalised. The PRAC agreed the MAH should terminate the ongoing 'European observational prospective study' specific obligation<sup>25</sup> as per the approved protocol. The PRAC advised that the marketing authorisation(s) should remain conditional.

## 8.3. Renewals of the marketing authorisation

### 8.3.1. Fenofibrate, pravastatin – PRAVAFENIX (CAP) - EMEA/H/C/001243/R/0020 (with RMP)

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Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Corinne Fechant

Scope: 5-year renewal of the marketing authorisation

## Background

Pravastatin is a HMG-CoA reductase inhibitor and in combination with fenofibrate, a fibrate is indicated for the treatment of high coronary heart disease (CHD)-risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose LDLC levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy.

Pravafenix, a centrally authorised medicine containing pravastatin/fenofibrate, was authorised in 2011.

The MAH submitted an application for the renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this five year-renewal with regard to safety and risk management aspects.

## Summary of advice

- Based on the review of the available pharmacovigilance data for Pravafenix and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal may be

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<sup>25</sup> European observational prospective study to evaluate the benefit/risk of vandetanib 300mg in RET mutation (-) and RET mutation (+) patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer

granted with unlimited validity. Despite the limited exposure of the medicinal product as a fixed dose combination, the two individual substances have a known safety profile. In addition, the PRAC acknowledged the importance of the planned post-authorisation safety study<sup>26</sup> to further characterise important risks as outlined in the RMP.

## 9. Product related pharmacovigilance inspections

### 9.1. List of planned pharmacovigilance inspections

None

### 9.2. List of planned pharmacovigilance inspections

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

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

### 10.1. Safety related variations of the marketing authorisation

#### 10.1.1. Mycophenolate mofetil – CELLCEPT (CAP) – EMEA/H/C/000082/II/0121

Applicant: Roche Registration Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.4 and 4.6 of the SmPC in order to add a warning for pregnant women and update the safety information related to pregnancy

#### Background

Mycophenolate mofetil is an immunosuppressive agent indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

A type II variation proposing to update the product information of Cellcept on safety information related to pregnancy is under evaluation at the CHMP. The PRAC was requested to provide a further advice on this variation. For background, see [PRAC minutes September 2015](#).

#### Summary of advice

- Based on the review of the available information, the PRAC reinforced the need to contraindicate the use of mycophenolate mofetil in pregnancy unless there is no suitable available alternative in view of the risks of transplant rejection.

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<sup>26</sup> European, observational, three-year cohort study on the safety of the fixed-dose combination pravastatin 40 mg/fenofibrate 160 mg in real clinical practice (FENOPRA-IV-14-1)



- The PRAC agreed the content of a DHPC including key advice to HCPs, and the need for a nationally-tailored approach to distribution of this letter in relation to off-label use. The PRAC also agreed the need for educational materials and a pregnancy exposure follow-up questionnaire that needs to be presented to national competent authorities and implemented within 4 months after the CHMP opinion. In terms of educational material, the PRAC agreed the key messages and that separate brochures should be provided to healthcare professionals and patients. Patient materials should be presented with appropriate distinguishing of the information for men and women.

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

None

## 10.3. Other requests

### 10.3.1. Antiretroviral medicinal products:

Abacavir –ZIAGEN (CAP) - EMEA/H/C/000252/LEG 089.1; abacavir, lamivudine – KIVEXA (CAP) - EMEA/H/C/000581/LEG 045.1; abacavir, lamivudine, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/LEG 090.1; atazanavir– REYATAZ (CAP) - EMEA/H/C/000494/LEG 080.1; darunavir – PREZISTA (CAP) - EMEA/H/C/000707/LEG 070.1; efavirenz – STOCRIN (CAP) - EMEA/H/C/000250/LEG 071.1, SUSTIVA (CAP) - EMEA/H/C/000249/LEG 080.1; efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/LEG 040.1; elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/LEG 014.1; emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/LEG 049.2; emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/LEG 043.1; emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/LEG 031.1; etravirine – INTELENCE (CAP) - EMEA/H/C/000900/LEG 048.1; fosamprenavir – TELZIR (CAP) - EMEA/H/C/000534/LEG 076.1; indinavir – CRIXIVAN (CAP) - EMEA/H/C/000128/LEG 039.1; lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/LEG 052.1, LAMIVUDINE VIIV (Art 58) - EMEA/H/W/000673/LEG 007.1; lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/LEG 038.1; lopinavir, ritonavir –ALUVIA (Art 58) - EMEA/H/W/000764/LEG 031.1, KALETRA (CAP) - EMEA/H/C/000368/LEG 118.1; nevirapine – VIRAMUNE (CAP) - EMEA/H/C/000183/LEG 061.1; rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/LEG 026.1; ritonavir – NORVIR (CAP) - EMEA/H/C/000127/LEG 049.1; saquinavir – INVIRASE (CAP) - EMEA/H/C/000113/LEG 065.1; stavudine – ZERIT (CAP) - EMEA/H/C/000110/LEG 060.1; tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/LEG 270.1; tipranavir - APTIVUS (CAP) - EMEA/H/C/000631/LEG 068.1

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Applicant: AbbVie Ltd (Kaletra, Norvir), Boehringer Ingelheim International GmbH (Aptivus, Viramune), Bristol-Myers Squibb Pharma EEIG (Reyataz, Sustiva, Zerit), Bristol-Myers Squibb and Gilead Sciences Ltd.(Atripla), Gilead Sciences International Ltd.(Emtriva, Eviplera, Stribild, Truvada, Tybost, Viread), Janssen-Cilag International N.V.(Edurant, Intelence, Prezista), Merck Sharp & Dohme Ltd (Crixivan, Isentress, Stocrin), Roche Registration Ltd. (Invirase), ViiV Healthcare UK Limited (Celsentri, Combivir, Epivir, Lamivudine Viiv, Kivexa, Telzir, Trizivir, Ziagen)

PRAC Rapporteur (lead): Qun-Ying Yue; PRAC Co-Rapporteur: Isabelle Robine; Julie Williams

Scope: Review of class labelling on mitochondrial dysfunction, lactic acidosis and lipodystrophy

## Background

Combination antiretroviral therapy (cART) consists of any combination regimen of antiretroviral medicines that include nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), with non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) or integrase inhibitors for the treatment of patients affected by the human immunodeficiency virus (HIV-1).

In the context of the ongoing procedures initiated in July 2014 reviewing new evidence with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy of antiretroviral medicines and their impact on the product information was reviewed. The PRAC concluded the review and provided advice to the CHMP. For further background, see [PRAC minutes June 2014](#), [PRAC minutes July 2014](#), [PRAC minutes March 2015](#) and [PRAC minutes September 2015](#).

## Summary of advice

- Following the report from the SAG-chair of the Scientific Advisory Group (SAG) HIV/viral held on 7 October 2015 and based on the review of the available information on lipodystrophy and lactic acidosis, the PRAC agreed that the lipodystrophy warning introduced in 2003 should be removed from the product information of all antiretroviral medicines while a specific warning related to lipoatrophy will be retained in the product information of stavudine-, zidovudine- and didanosine-containing products. In addition, the lactic acidosis warning, introduced in 2001, should be removed from the product information of emtricitabine, lamivudine, abacavir-containing regimens and tenofovir-containing products, although, where applicable, the product information will still state that very rare cases have been reported. The product-specific boxed warning should remain for zidovudine-, didanosine- and stavudine-containing products. Relevant MAHs will update the product information accordingly relating to lactic acidosis and lipoatrophy. The evaluation of mitochondrial dysfunction is still ongoing.

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

### 11.1. Safety related variations of the marketing authorisation

#### 11.1.1. Hydroxyethyl starch (NAP) - DE/H/xxx/WS/266, SE/H/xxx/WS/268

Applicant: Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue, Martin Huber

Scope: PRAC consultation on two safety variations (DE/H/xxx/WS/266 and SE/H/xxx/WS/268) related to draft protocols for two Phase IV clinical studies on trauma and surgery patients imposed as the outcome of the article 107i referral

## Background

Hydroxyethyl starch (HES) is a non-ionic starch derivative indicated for the treatment of patients with hypovolaemia caused by acute blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone are not considered to be sufficient under certain conditions.

As part of the conclusions of the review of HES-containing products in the framework of a safety referral under Article 107i of Directive 2001/83/EC ([EMA/H/A-107i/1376](#)), MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted respectively two study protocols for a Phase IV clinical trials in perioperative setting (elective abdominal surgery) and a second clinical trial in trauma setting treated with poly (o-2-hydroxyethyl) starch as part of national MRP variations. Germany and Sweden, as respective RMS, requested PRAC to provide advice to Member States on their preliminary assessments of the study protocols.

### Summary of advice

- Based on the review of the available information, the PRAC agreed with the preliminary conclusions from the RMS that the study protocols could be approvable, provided that satisfactory responses are provided by the MAHs following a request for supplementary information.
- The PRAC considered that the choice of the 6% solution may be reasonable for the clinical trials as it is the most commonly used presentation and that the study results might be extrapolated to the 10% solution if a higher risk of mortality and renal failure is confirmed. Conversely, if the results of the proposed studies exclude significant differences in risks, doubts will still remain that a higher concentration (10%) of HES may be more harmful than the lower concentration (6%). Furthermore, the PRAC agreed that for products containing HES with molecular weights other than 130 kDa<sup>27</sup> the transferability of the results should be considered limited. In terms of sample size in the 'trauma trial', the PRAC expressed concerns on the limited size proposed by the MAHs and supported the RMS's proposal to request an increase in the number of recruiting centres as well as a more sensitive primary composite endpoint. With regard to the protocols for the 'surgery clinical trial', the PRAC agreed that the primary endpoint was acceptable. Finally, the PRAC underlined the need for the MAHs to provide National Competent Authorities with regular updates on the status of recruitment for both clinical trials.

## 11.2. Other requests

### 11.2.1. Antiretroviral medicinal products (NAP)

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Applicant: Teva Pharma B.V., Mickle-Pharm GmbH

PRAC Rapporteur: Martin Huber

Scope: PRAC consultation on initial marketing authorisation applications for generic medicinal products and the need for the applicants to participate in the Antiretroviral Pregnancy Registry

### Background

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<sup>27</sup> Kilo Daltons

Antiretroviral agents are indicated for the treatment of patients affected by the human immunodeficiency virus (HIV) under certain conditions.

The Antiretroviral Pregnancy Registry (APR) was set up to detect an early signal of any major teratogenic effect associated with a prenatal exposure to the antiretroviral medicinal products monitored through the registry. All originator medicinal products participate in the registry and their product information, in particular, section 4.6 entitled 'fertility, pregnancy and lactation' is updated with any relevant information as appropriate.

In the context of the evaluation of marketing authorisation applications for generic medicinal products at national level, Germany sought the advice of the PRAC regarding the relevance for all MAHs and applicants of generic medicinal products to participate in the registry. Following the PRAC request in September 2015 to gather further information on the APR data collection and participating MAHs, the PRAC further discussed the issue and adopted advice to the Member States. For further background, see [PRAC minutes September 2015](#).

### Summary of advice

- Based on the review of the available data and further information gathered on the APR data collection, participating MAHs and report generation, the PRAC concurred that adding the APR as an additional pharmacovigilance activity in the RMP of individual medicinal product needs to be considered in the light of whether there are specific questions linked to safety concerns associated with the product under review that are expected to be addressed by the registry. Therefore, the addition of the APR to the RMP as an additional pharmacovigilance activity should be considered on a case-by-case basis as a matter of assessment.

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

### 12.2. Coordination with EMA Scientific Committees or CMDh-v

#### 12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population

PRAC lead: Jolanta Gulbinovič, Amy Tanti

**Action:** For discussion

The EMA secretariat presented to PRAC the draft guideline on the conduct of pharmacovigilance for medicines used by the paediatric population (revision 2), following previous discussion and adoption of the concept paper to revise the guideline, in April 2014 and first review of the draft guideline at the level of the Paediatric Committee (PDCO) last August. The PRAC discussed several aspects, in particular the link between long term safety concerns identified by PDCO at the time of PIP assessment and RMP as well as risk communication to the paediatric population including age appropriate educational materials. PRAC delegates were invited to provide written comments by 31 October 2015, for inclusion into an updated draft guideline. This updated draft guideline is due for adoption at PRAC in

November/December 2015 (and PDCO in December 2015). It will be subsequently released for a 3 month-public consultation.

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

None

### **12.4. Cooperation within the EU regulatory network**

None

### **12.5. Cooperation with International Regulators**

#### **12.5.1. Confidentiality arrangements with third country regulators and organisations - Update**

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The PRAC was informed that two confidentiality arrangements have been concluded by the European Commission and EMA in July and September 2015 respectively; the first with Swissmedic<sup>28</sup> and the second with the World Health Organization (WHO). Both arrangements are established for an initial period of 5 years and may be renewed. Confidentiality agreements are already in place between EMA and the following international partners: US FDA<sup>29</sup>, Japan PMDA/MHLW<sup>30</sup>, Health Canada and TGA<sup>31</sup> Australia. Under the terms of confidentiality or working arrangements, the parties to the arrangement agree not to disclose non-public information, which means that product related information can be shared between the parties. The arrangements also facilitate ad hoc participation at product related discussions in response to specific requests.

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

#### **12.6.1. Consortium on progressive multifocal leukoencephalopathy (PML) - progress update**

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At the organisational matters teleconference on 22 October 2015, the EMA Secretariat presented an update on the progress with the consortium on progressive multifocal leukoencephalopathy (PML), established in 2009 and focusing on methods to enable prediction and prevention of PML associated with immunomodulatory and immunosuppressive treatments which published a paper<sup>32</sup> on PML. The EMA/NCA regulators also published in September 2015 an article<sup>33</sup> on strategy in regulatory decision-making for PML risk management.

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<sup>28</sup> Swiss Agency for Therapeutic Products

<sup>29</sup> Food and Drug Administration

<sup>30</sup> Pharmaceuticals and Medical Devices Agency/Ministry of Health, Labour and Welfare

<sup>31</sup> Therapeutic Goods Administration

<sup>32</sup> Pavlovic D, Patera AC, Nyberg F, Gerber M et al. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Therapeutic Advances in Neurological Disorders* November 2015 vol. 8 no. 6 255-273

<sup>33</sup> Segec A, Keller-Stanislawski B, Vermeer NS, Macchiarulo C, Straus SM, Hidalgo-Simon A, De Bruin ML. Strategy in regulatory decision-making for management of progressive multifocal leukoencephalopathy. *Clinical pharmacology and therapeutics*. September 2015 DOI: 10.1002/cpt.199

## 12.6.2. Innovative Medicines Initiative (IMI) project - ADAPT-SMART

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The EMA Secretariat presented to PRAC the ADAPT-SMART (accelerated development of appropriate patient therapies) consortium project corresponding to a platform for the coordination of medicines adaptive pathways with patients' activities and perspectives. The project seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion. The project is composed of four work packages and PRAC delegates were invited to express interest in participating in work package 1 on 'evidence generation throughout the life cycle' by 16 October 2015.

## 12.6.3. Strategic review and learning meetings organised during the term of the European presidency: organisational aspects; clarification on responsibility for handling of declared interests and on involvement of external (non NCA) speakers

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At the organisational matters teleconference on 22 October 2015, the EMA Secretariat presented two guidance documents on the organisation of Strategic Review and Learning Meetings under European Presidency: one covering organisational aspects and the other clarifying the responsibilities for handling declared interests and the involvement of external speakers. PRAC delegates were invited to provide comments on these two guidance documents by 5 November 2015.

## 12.6.4. World Health Organization(WHO) - Biological qualifier update

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The EMA Secretariat presented an update on the World Health Organization (WHO) biological qualifier. The biological qualifier scheme was put forward to address the pressure arising from MAHs of biosimilar medicines, the unilateral use of international non-proprietary (INN)-like names in some jurisdictions, local needs to support prescribing of biosimilars and for traceability purposes relating to pharmacovigilance. The final draft proposal was released for public consultation in July 2015 and consists of a 4 letter code (random) assigned to the MAH including site information for all biologicals (retrospective) and is separate from the INN policy. The comments raised by EMA on the initial draft proposal released for public consultation in July 2014 were presented to the PRAC. EMA is now planning on reinforcing the same comments in the new public consultation on the final draft proposal. PRAC delegates were invited to provide comments by 16 October 2015.

## 12.7. PRAC work plan

### 12.7.1. PRAC work plan 2016 - development

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At the organisational matters teleconference on 22 October 2015, the EMA Secretariat presented to the PRAC a short update on the development of the draft 2016 PRAC work plan. PRAC members welcomed the progress made and offered ongoing support in this important exercise.

## 12.8. Planning and reporting

None

## **12.9. Pharmacovigilance audits and inspections**

### **12.9.1. Pharmacovigilance systems and their quality systems**

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

### **12.10.1. Periodic safety update reports**

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None

### **12.10.2. Granularity and Periodicity Advisory Group (GPAG)**

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None

### **12.10.3. Project and Maintenance Group (PMG) 2 - roadmap for PSUR issues**

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At the organisational matters teleconference on 22 October 2015, the EMA Secretariat presented to the PRAC a roadmap for addressing PSUR issues, including assessment aspects, particularly with regard to PSUSAs covering nationally approved products only. A subgroup composed of PRAC and CMDh delegates and EMA members has started working on a scoping paper focussing on the life-cycle concept, level of evidence and approach to critical appraisal, to support benefit risk evaluation and any proposed labelling changes, including an action plan, taking into account the upcoming PRAC training for assessors organised in November 2015 and a workshop with industry and NCA assessors planned early 2016. Further updates will be provided in due course.

### **12.10.4. PSURs repository**

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None

### **12.10.5. Union reference date list – consultation on the draft list**

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The PRAC endorsed the draft revised EURD list version October 2015 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations.

Post-meeting note: following the PRAC meeting in October 2015, the updated EURD list was adopted by the CHMP and CMDh at their October 2015 meeting and published on the EMA website on 30/10/2015, see:

## **12.11. Signal management**

### **12.11.1. Medical literature monitoring (MLM) update**

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In line with [GVP Module VI](#) on 'management and reporting of adverse reactions to medicinal products', the EMA is conducting the monitoring of medical literature and the entry of relevant information into EudraVigilance in order to enhance efficiency, provide simplification, improve data quality and better support signals management within the EU.

At the organisational matters teleconference on 22 October 2015, the EMA Secretariat updated the PRAC on the medical literature monitoring (MLM) service launched on 1 July 2015, following a set-up phase that included creating search parameters for selected substance groups in selected literature databases and creating tracking tools. Since 1 September 2015, MLM has entered its full production phase where the substance groups have increased to 100 herbal substances and 300 chemical substances groups based on a refined target strategy and regular searches in the EMBASE<sup>34</sup> and EBSCO<sup>35</sup> literature databases. A description was provided on the processing and follow-up of individual cases in EudraVigilance related to suspected adverse reactions identified in the scientific and medical literature. Future updates will be provided in due course.

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

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The PRAC was updated on the outcome of the October 2015 SMART Working Group (SMART WG). The SMART WG discussed the designated medical events (DLE) list and consideration regarding transparency aspects. Further discussion is planned in November 2015. In addition, the SMART WG discussed how to best define the confirmation step for signals handled in other procedures. Finally, the SMART WG discussed the outline of the upcoming revision of GVP module IX on signal management planned in 2016.

## **12.12. Adverse drug reactions reporting and additional reporting**

### **12.12.1. Management and reporting of adverse reactions to medicinal products**

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None

### **12.12.2. Additional monitoring**

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None

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<sup>34</sup> Biomedical and pharmacological database of published literature

<sup>35</sup> Provider of scientific and medical library database services



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

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

Post-meeting note: The updated additional monitoring list was published on 26/10/2015 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#))

## 12.13. EudraVigilance database

### 12.13.1. Activities related to the confirmation of full functionality – EudraVigilance audit plan

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In line with Regulation (EC) 726/2004 stipulating that the EMA should set up and maintain a pharmacovigilance database and data processing network ('EudraVigilance (EV) database'), the EMA Secretariat presented to PRAC the upcoming EV audit plan. To this effect, the EMA will open a call for tender to pre-selected audit companies to conduct such activity in 2016 which will report to the PRAC and ultimately to the EMA Management Board. Regular updates to PRAC will be planned in accordance with the audit plan.

### 12.13.2. EudraVigilance Access Policy

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The EMA Secretariat presented to PRAC the draft revised EudraVigilance access policy following the public consultation held in 2014. The EMA provided PRAC with an overview of the main comments received and their implementation in the revised policy. The PRAC adopted the revised access policy. The policy is planned for adoption by the EMA Management board in December 2016 before coming into force.

## 12.14. Risk management plans and effectiveness of risk minimisations

### 12.14.1. Risk management systems

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None

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

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None

## 12.15. Post-authorisation safety studies (PASS)

### 12.15.1. Post-authorisation Safety Studies – imposed PASS

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None

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

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None

## **12.16. Community procedures**

### **12.16.1. Referral procedures for safety reasons**

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None

## **12.17. Renewals, conditional renewals, annual reassessments**

None

## **12.18. Risk communication and transparency**

### **12.18.1. Public participation in pharmacovigilance**

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None

### **12.18.2. Safety communication**

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None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

None

## **13. Any other business**

### **13.1. Good Pharmacovigilance Practice (GVP) Chapter P.II. on biologicals**

The PRAC was presented with an outline of the draft GVP product- or population-specific considerations II on biological medicinal products. The draft document will be revised based on comments from committees and working parties consulted, released for public consultation and further discussed at PRAC before finalisation.

### **13.2. Good Pharmacovigilance Practice (GVP) Module XII on safety-related actions on authorised medicinal products**

At the organisational matters teleconference on 22 October 2015, the EMA Secretariat presented to the PRAC an update on the draft GVP module XII on safety-related actions on authorised medicinal products. The PRAC considered that most content was covered in other GVP modules or other guidance, and if not but necessary, could be integrated in the revision of other GVP modules.

### **13.3. Post-authorisation efficacy studies – first draft scientific guidance**

At the organisational matters teleconference on 22 October 2015, the EMA secretariat presented the revised draft scientific guidance on post-authorisation efficacy studies (PAES) developed in accordance with Article 108a of Directive 2001/83/EC, and indicated that most PRAC comments have been implemented. The guideline outlines how PAES, imposed or not imposed, should be designed by companies to support regulatory decision making in the EU. The PRAC adopted the guidance, due for CHMP and CMDh endorsement before its release for a 3 month public consultation ([EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015](#)), until 31/01/2016) along a [PAES questions and answers](#) to address regulatory aspects for the fulfilment of imposed PAES. The PRAC welcomed the progress and looked forward to the outcome of public consultation.

### **13.4. Update on Pharmacovigilance systems and services**

The PRAC was updated on the revised implementation governance of the pharmacovigilance legislation, adopted by the Heads of Medicines Agencies (HMA), and the pharmacovigilance programme. The EMA Secretariat presented the [Pharmacovigilance Programme Update \(fifth edition dated October 2015\)](#).

### **13.5. Good Pharmacovigilance Practice (GVP) Guideline on product or population specific considerations III: pregnancy and breastfeeding – concept paper**

The EMA Secretariat presented to PRAC a concept paper to be used as a basis to develop a GVP module on 'Product- or Population specific considerations III: pregnancy and breastfeeding' aiming at defining the key elements and challenges of optimising pharmacovigilance practice for medicines used in women of childbearing potential and effects of medicines taken by men, in relation to reproduction, including medicines taken during pregnancy, medicines taken during breastfeeding as well as long term effects of medicines taken before and during pregnancy, and effects of medicines taken during breastfeeding on infants, children and adolescents. The PRAC discussed several aspects, in particular relating to case definition and use of pregnancy registries. The PRAC adopted the concept paper that will be further discussed at CHMP for adoption. The PRAC will be consulted on the draft GVP module in Q2 2016.

## 14. Annex I – Risk Management Plans

### 14.1. 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 will be made available following the CHMP opinion on their marketing authorisation(s).

#### 14.1.1. Atazanavir - EMEA/H/C/004048

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Generic

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

#### 14.1.2. Caspofungin - EMEA/H/C/004134

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Generic

Scope: Treatment of invasive candidiasis and invasive aspergillosis

#### 14.1.3. Human heterologous liver cells – HEPARESC (CAP MAA) - EMEA/H/C/003750, Orphan

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Applicant: Cytonet GmbH&Co KG

Scope: Treatment of urea cycle disorders (UCD)

#### 14.1.4. Insulin human - EMEA/H/C/003858

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Scope: Treatment of diabetes

#### 14.1.5. Lopinavir, ritonavir - EMEA/H/C/004025

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Generic

Scope: Treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years

#### 14.1.6. Pemetrexed - EMEA/H/C/004109

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Hybrid

Scope: Treatment of malignant pleural mesothelioma and non-small cell lung cancer

#### 14.1.7. Pitolisant - EMEA/H/C/002616, Orphan

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Applicant: Bioprojet Pharma

Scope: Treatment of narcolepsy

## **14.2. Medicines in the post-authorisation phase – PRAC-led procedure**

None

## **14.3. Medicines in the post-authorisation phase – PRAC-led procedures**

### **14.3.1. Imatinib – GLIVEC (CAP) - EMEA/H/C/000406/II/0098/G**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of a revised RMP in order to exclude the potential drug interactions with acetaminophen/paracetamol and imatinib, exclude the elderly population as missing information. In addition, the RMP is updated with the safety actions taken since the last update including drug rash with eosinophilia and system symptoms, gastric antral vascular ectasia and chronic renal failure. Finally, the RMP is updated with amended due dates of final study reports for three category 3 studies: CSTI571A2405, CSTI571A2403 and CSTI571L2401

### **14.3.2. Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – PANDEMRIX (CAP) - EMEA/H/C/000832/II/0079**

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Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Rafe Suvarna

Scope: Update of Annex II of the product information in order to delete the obligation to perform non-clinical mechanistic studies in naïve or A(H1N1) pdm09 primed 4-week old female cotton rats to evaluate the potential disruption of blood-brain-barrier integrity and the potential CNS inflammation/damage following intramuscular administrations of Pandemrix, of non-adjuvanted H1N1 antigen and of AS03 adjuvant system

## **14.4. Medicines in the post-authorisation phase – CHMP-led procedure**

### **14.4.1. Afatinib – GIOTRIF (CAP) - EMEA/H/C/002280/II/0012**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of squamous histology progressing on or after platinum-based chemotherapy for Giotrif. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

### **14.4.2. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0041**

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include an expanded therapeutic indication for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1). In addition, the MAH took the opportunity to

update Annex II to reflect a change in the PSUR cycle. The Package leaflet is proposed to be updated accordingly

#### 14.4.3. Anidulafungin – ECALTA (CAP) - EMEA/H/C/000788/II/0030 (without RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Submission of final study results of study A8851030: retrospective cohort study of the risk of severe hepatic injury in hospitalised patients treated with echinocandins for candida infections

**Action:** For adoption of a clock-stop extension

#### 14.4.4. Bevacizumab – AVASTIN (CAP) - EMEA/H/C/000582/II/0086

Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to extend the use of bevacizumab in combination with erlotinib for the first line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations. As a consequence sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP are updated accordingly

#### 14.4.5. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/002455/II/0025

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include a new indication for brentuximab vedotin for the treatment of adult patients at increased risk of relapse or progression following autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly

#### 14.4.6. Brentuximab vedotin – ADCETRIS (CAP) - EMEA/H/C/002455/II/0028

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the 50mg powder for concentrate for solution SmPC in order to update the safety information based on study SGN35-006 part A to allow retreatment of adult patients who have responded to previous treatment with brentuximab vedotin under the existing indications of: 1) relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option and for adult patients with or 2) relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)

#### 14.4.7. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/II/0059

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC to include information related to the treatment of Dupuytren's contracture with 2 concurrent injections of collagenase clostridium histolyticum. The Package Leaflet and RMP are updated accordingly

#### **14.4.8. Crizotinib – XALKORI (CAP) - EMEA/H/C/002489/II/0024**

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Applicant: Pfizer Limited

PRAC Rapporteur: Corinne Fechant

Scope: Extension of indication to the first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC): update of section 4.1 of the SmPC. In addition update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to include the results of the pivotal study A8081014: a multinational, multicentre, randomized, open-label, phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC and updated safety results from studies A8081001, A8081005 and A8081007. In addition, section 5.1 of the SmPC was revised to include updated overall survival data from studies A8081001 and A8081005

#### **14.4.9. Daptomycin – CUBICIN (CAP) - EMEA/H/C/000637/II/0053/G**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to extend the age range for the indication 'complicated skin and soft-tissue infections' (cSSTI) to include paediatric patients from 1 to 17 years of age. As a consequence sections 4.1, 4.2, 4.4, 5.2 and 6.2 of the SmPC are being updated. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 9.0 has been submitted accordingly

#### **14.4.10. Empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/WS/0800; linagliptin, metformin – JENTADUETO (CAP) - EMEA/H/C/002279/WS/0800**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to align it for Jentaduetto and Synjardy to the recently modified SmPC for the UK metformin label (Glucophage). The RMPs (version 3.0 for Synjardy and version 11.0 for Jentaduetto) have been updated accordingly

#### **14.4.11. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/WS/0801 empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/WS/0801**

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Applicant: Boehringer Ingelheim International GmbH, Boehringer Ingelheim GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to update the renal development and maturation information after analysis of the non-clinical study 14R018 [n00231757] entitled '10-week toxicity study by oral gavage in the juvenile Wistar Han rat with a 13-week recovery'

#### 14.4.12. Human hepatitis B immunoglobulin – ZUTECTRA (CAP) - EMEA/H/C/001089/II/0024

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Applicant: Biotest Pharma GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to the prevention of hepatitis B virus (HBV) re-infection in hepatitis B antigen (HBsAg) and HBV-DNA negative patients at least one week – instead of the approved at least 6 months - after liver transplantation for hepatitis B induced liver failure. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the rMP are updated accordingly

#### 14.4.13. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0007/G

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Group of variations to submit several non-clinical studies reports. Accordingly, update of section 4.5 of the SmPC regarding BRCP inhibition, update of section 4.5 of the SmPC to delete the CYP3A4 inhibition statement, update of the wording regarding the co-administration with transport substrates/inhibitors in section 5.2 of the SmPC. The Package Leaflet and the RMP are updated accordingly

#### 14.4.14. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0011

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Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Extension of indication to include a new indication for Zydelig to include the combination of idelalisib with ofatumumab. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly

#### 14.4.15. Measles, mumps, rubella and varicella vaccine (live) – PROQUAD (CAP) - EMEA/H/C/000622/R/0100

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Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

#### 14.4.16. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0002

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment as monotherapy of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults patients based on study CA209057. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. Furthermore, SmPC section 4.8 has been revised with updated combined clinical trial exposure numbers to reflect inclusion of studies in non-squamous NSCLC and in nivolumab in combination with ipilimumab in advanced melanoma. The Package Leaflet and RMP (version 3.0) are updated accordingly.



#### 14.4.17. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0003

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment in combination with ipilimumab of advanced (unresectable or metastatic) melanoma in adults based on interim data from study CA209067 and the final clinical study report of study CA209069. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet and RMP (version 3.0) are updated accordingly. The application includes a paediatric non-clinical biomarker study provided to fulfil paediatric requirements.

#### 14.4.18. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0004

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on toxic epidermal necrolysis (TEN) and encephalitis. The Package Leaflet is updated accordingly

#### 14.4.19. Ofatumumab – ARZERRA (CAP) - EMEA/H/C/001131/II/0041

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Extension of indication to include the maintenance therapy in chronic lymphocytic leukemia (CLL). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The MAH is also taking the opportunity of this procedure to update the Annex II and combine the 2 SmPCs for the 100 mg and 1,000mg vials

#### 14.4.20. Oritavancin – ORBACTIV (CAP) - EMEA/H/C/003785/II/0003

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Applicant: The Medicines Company UK Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to include information on the interaction potential between oritavancin and phospholipid-dependent and phospholipid-independent laboratory coagulation tests following the conclusion of two RMP category 3 studies. The Package Leaflet and RMP are updated accordingly

#### 14.4.21. Regorafenib – STIVARGA (CAP) - EMEA/H/C/002573/II/0014/G

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.4 of the SmPC in order to delete the warnings and precautions information on KRAS mutant tumours patients after analysis of the provided study report for the CONCUR study (15808) (ANX 002.4 and 002.3). In addition the MAH has submitted results of the CORRECT trial (14387) as final biomarker analysis of the study. The obligation to conduct post-authorisation measures in Annex II has been updated in line with the presented studies

#### 14.4.22. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/II/0037

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of a clinical study report (CSR) for the terminated post-authorisation efficacy study (PAES) PTG116878 entitled 'a dose-optimization study of ezogabine/retigabine immediate release tablets versus placebo in the adjunctive treatment of subjects with partial-onset seizures' in order to evaluate the efficacy of retigabine immediate release as an adjunctive treatment for partial-onset seizures in adults with epilepsy who have inadequate control of their seizures with a single antiepileptic drug. As a consequence a revised RMP (version 13.1) is submitted accordingly

#### 14.4.23. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/II/0038

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of a clinical study report (CSR) for the terminated post-authorisation efficacy study (PAES) RTG114855 entitled 'a randomised, double-blind, placebo-controlled, parallel-group, multicentre study to determine the efficacy and safety of 2 doses of retigabine immediate release (900 mg/day and 600 mg/day) used as adjunctive therapy in adult Asian subjects with drug-resistant partial-onset seizures' in order to investigate the efficacy, safety and tolerability and health outcomes of Asian subjects with drug-resistant partial onset seizures (POS). As a consequence, a revised RMP (version 13.2) is submitted accordingly

#### 14.4.24. Rilpivirine – EDURANT (CAP) - EMEA/H/C/002264/II/0017/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include the treatment of antiretroviral (ARV) treatment-naïve paediatric patients aged 12 to <18 years based on the results of the 48-week data of study TMC278-TiDP38-C213 (PAINT), undertaken to evaluate the pharmacokinetics, safety/tolerability, and efficacy of rilpivirine (RPV) 25 mg qd in combination with an investigator-selected background regimen containing 2 nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) in this adolescent population. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet and RMP (version 6.0) are updated accordingly

#### 14.4.25. Ruxolitinib – JAKAVI (CAP) - EMEA/H/C/002464/II/0024

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a warning on reported cases of Merkel cell carcinoma in patients treated with ruxolitinib. The RMP is updated accordingly

#### 14.4.26. Saquinavir – INVIRASE (CAP) - EMEA/H/C/000113/II/0115

Applicant: Roche Registration Ltd

PRAC Rapporteur: Marianne Lunzer

Scope: Update of section 4.5 the SmPC in order to update the drug-drug interaction information and to delete information regarding the use of unboosted invirase. The Package Leaflet is updated accordingly. The RMP is included as a consolidated version as requested as part of the last PSUR (PSUSA/00002684/201412)

#### 14.4.27. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/II/0001/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate as monotherapy or in combination with methotrexate (MTX). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet and the RMP are updated accordingly

#### 14.4.28. Secukinumab – COSENTYX (CAP) - EMEA/H/C/003729/II/0002

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to add the treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. Consequently SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The Package Leaflet and RMP have been updated accordingly

#### 14.4.29. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - EMEA/H/C/000674/X/0085

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Line extension to add the 'intramuscular' route of administration for all presentations

#### 14.4.30. Simeprevir – OLYSIO (CAP) - EMEA/H/C/002777/II/0015

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to amend the safety information regarding the use of simeprevir in interferon-free regimens, based on the primary analysis (SVR12) of studies HPC3017 and HPC3018. The Package Leaflet and Labelling are updated accordingly

#### 14.4.31. Voriconazole – VFEND (CAP) - EMEA/H/C/000387/II/0110/G

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of the SmPC sections 4.4, 4.8 and 5.1 to reflect the safety and efficacy data from studies in paediatric population. The Package Leaflet and the RMP (version 4) are updated accordingly

## **15. 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).

### **15.1. PSUR procedures including centrally authorised products only**

#### **15.1.1. Afatinib – GIOTRIF (CAP) - PSUSA/10054/201503**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **15.1.2. Albiglutide – EPERZAN (CAP) - PSUSA/10175/201503**

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Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### **15.1.3. Alemtuzumab – LEMTRADA (CAP) - PSUSA/10055/201503**

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Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

#### **15.1.4. Aminolevulinic acid – GLIOLAN (CAP) - PSUSA/00009/201503**

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Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

#### **15.1.5. Apremilast – OTEZLA (CAP) - PSUSA/10338/201503**

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Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

#### **15.1.6. Aprepitant – EMEND (CAP) - PSUSA/00229/201503**

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **15.1.7. Atosiban – TRACTOCILE (CAP) - PSUSA/00264/201501**

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Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### **15.1.8. Bedaquiline – SIRTURO (CAP) - PSUSA/10074/201503**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### **15.1.9. Belimumab – BENLYSTA (CAP) - PSUSA/09075/201503**

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **15.1.10. Cholic acid – KOLBAM (CAP) - PSUSA/10182/201504**

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Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure (MA withdrawal dated 11 June 2015)

#### **15.1.11. Cholic acid - ORPHACOL (CAP) - PSUSA/10208/201503**

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Applicant: Laboratoires CTRS - Boulogne Billancourt

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

#### 15.1.12. Dabigatran – PRADAXA (CAP) - PSUSA/00918/201503

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

#### 15.1.13. Dexmedetomidine – DEXDOR (CAP) - PSUSA/00998/201503

Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.14. Dulaglutide – TRULICITY (CAP) - PSUSA/10311/201503

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

#### 15.1.15. Emtricitabine – EMTRIVA (CAP) - PSUSA/01209/201504

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

#### 15.1.16. Emtricitabine, tenofovir – TRUVADA (CAP) - PSUSA/01210/201504

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.17. Everolimus – VOTUBIA (CAP) - PSUSA/01343/201503

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 15.1.18. Fenofibrate, simvastatin – CHOLIB (CAP) - PSUSA/10096/201502

Applicant: BGP Products Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.19. Fosaprepitant – IVMEND (CAP) - PSUSA/01471/201503

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 15.1.20. Glycopyrronium bromide, indacaterol – ULTIBRO BREEZHALER (CAP), ULUNAR BREEZHALER (CAP), XOTERNA BREEZHALER (CAP) - PSUSA/10105/201503

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

#### 15.1.21. Influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted) – FOCETRIA (CAP) - PSUSA/02278/201503

Applicant: Novartis Vaccines and Diagnostics S.r.l.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure (MA expired on 13/08/2015)

#### 15.1.22. Insulin degludec, liraglutide – XULTOPHY (CAP) - PSUSA/10272/201503

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 15.1.23. Japanese encephalitis virus (inactivated) – IXIARO (CAP) - PSUSA/01801/201503

Applicant: Valneva Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 15.1.24. Lapatinib – TYVERB (CAP) - PSUSA/01829/201503 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 15.1.25. Methylnaltrexone bromide – RELISTOR (CAP) - PSUSA/02023/201503

Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

#### 15.1.26. Naloxegol – MOVENTIG (CAP) - PSUSA/10317/201503

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Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### 15.1.27. Raltegravir –ISENTRESS (CAP); raltegravir, lamivudine - DUTREBIS (CAP) - PSUSA/02604/201503

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.28. Retigabine – TROBALT (CAP) - PSUSA/02624/201503

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### 15.1.29. Riociguat – ADEMPAS (CAP) - PSUSA/10174/201503

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.30. Rivaroxaban – XARELTO (CAP) - PSUSA/02653/201503

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### 15.1.31. Telaprevir – INCIVO (CAP) - PSUSA/09306/201503

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### 15.1.32. Telavancin – VIBATIV (CAP) - PSUSA/02879/201503

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Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure



#### 15.1.33. Tolcapone – TASMAR (CAP) - PSUSA/02985/201503 (with RMP)

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### 15.1.34. Trastuzumab – HERCEPTIN (CAP) - PSUSA/03010/201503

Applicant: Roche Registration Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 15.1.35. Vortioxetine – BRINTELLIX (CAP) - PSUSA/10052/201503 (with RMP)

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

#### 15.1.36. Zonisamide – ZONEGRAN (CAP) - PSUSA/03152/201503

Applicant: Eisai Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

### **15.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)**

#### 15.2.1. Cladribine – LITAK (CAP), NAP - PSUSA/00787/201502

Applicant: Lipomed GmbH, various

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

#### 15.2.2. Travoprost – IZBA (CAP), TRAVATAN (CAP), NAP - PSUSA/03011/201502

Applicant: Alcon Laboratories (UK) Ltd, various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

### **15.3. PSUR procedures including nationally approved products (NAPs) only**

#### **15.3.1. Cilazapril, cilazapril hydrochlorothiazide (NAP) - PSUSA/00000749/201502**

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Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### **15.3.2. Fluocinolone acetonide (intravitreal implant in applicator) (NAP) - PSUSA/00010224/201502**

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Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

#### **15.3.3. Iloprost (intravenous solution) (NAP) - PSUSA/00009190/201501**

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Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

#### **15.3.4. Lisdexamfetamine (NAP) - PSUSA/00010289/201502**

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Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### **15.3.5. Mesalazine (NAP) - PSUSA/00001990/201502**

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Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### **15.3.6. Methysergide (NAP) - PSUSA/00002030/201502**

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Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **15.3.7. Nafarelin (NAP) - PSUSA/00002105/201502**

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Applicant: various

PRAC Lead: Ingebjørg Buajordet

Scope: Evaluation of a PSUSA procedure

#### **15.3.8. Nitrofurantoin, nifurtoinol (NAP) - PSUSA/00002174/201502**

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Applicant: various

PRAC Lead: Jolanta Gulbinovic

Scope: Evaluation of a PSUSA procedure

#### **15.3.9. Olodaterol (NAP) - PSUSA/00010245/201503**

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Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **15.3.10. Sevoflurane (NAP) - PSUSA/00002698/201501**

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Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### **15.3.11. Tenonitrozole (NAP) - PSUSA/00003185/201502**

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Applicant: various

PRAC Lead: Nicolae Fotin

Scope: Evaluation of a PSUSA procedure

#### **15.3.12. Tiludronic acid (NAP) - PSUSA/00002959/201502**

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Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

#### **15.3.13. Vancomycin (NAP) - PSUSA/00003097/201501**

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Applicant: various

PRAC Lead: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

### **15.4. Follow-up to PSUR procedures**

None

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

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

### 16.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>36</sup>

#### 16.1.1. Thiocolchicoside (NAP) - EMEA/H/N/PSP/j/0030

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Applicant: Sanofi-Aventis Recherche & Développement and other companies involved in the consortium

PRAC Rapporteur: Amelia Cupelli

Scope: Drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription

### 16.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>37</sup>

#### 16.2.1. Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/MEA/026, VALDOXAN (CAP) - EMEA/H/C/000915/MEA/026

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Applicant: Servier (Ireland) Industries Ltd, Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: PASS protocol for study CLE-20098-96-096: a non-interventional post-authorisation safety study: agomelatine drug utilisation study (DUS) in selected European countries: a multinational, observational study to assess effectiveness of risk-minimisation measures

#### 16.2.2. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA/002.2

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Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 002.1 (PASS protocol for an observational study of the risk of acute pancreatitis in subjects exposed to albiglutide, other GLP-1 agonists or DPP-4 inhibitors compared to other antidiabetic agents (protocol PRJ2335)) request for supplementary information (RSI) as adopted in April 2015

#### 16.2.3. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA/003.2

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Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

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<sup>36</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>37</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

Scope: MAH's response to MEA 003.1 (PASS protocol for a study to assess the risk of thyroid and pancreatic cancers, and malignancy when used in combination with insulins in observational databases of sufficient size that provides long term longitudinal follow up of patients (protocol PRJ2331)) request for supplementary information (RSI) as adopted in April 2015

#### 16.2.4. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA/004.2

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 004.1 (PASS protocol for a cohort study to investigate the prescribing of albiglutide among women of child bearing age who have type 2 diabetes (Protocol PRJ2376)) request for supplementary information (RSI) as adopted in April 2015

#### 16.2.5. Albiglutide – EPERZAN (CAP) - EMEA/H/C/002735/MEA/005.2

Applicant: GlaxoSmithKline Trading Services

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 005.1 (PASS protocol for a retrospective cohort study to assess the utilisation of albiglutide among women of child bearing age in the U.S. (protocol PRJ2379)) request for supplementary information (RSI) as adopted in April 2015

#### 16.2.6. Dasabuvir – EXVIERA (CAP) - EMEA/H/C/003837/MEA/001.1

Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's responses to MEA001 (PASS protocol for a prospective, observational cohort study utilising the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (3 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (2-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA Regimens in a real world setting) as adopted in April 2015

#### 16.2.7. Desloratadine – AERIUS (CAP) - EMEA/H/C/000313/MEA/065; AZOMYR (CAP) - EMEA/H/C/000310/MEA/065; NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA/065

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of a new protocol for a PASS: 'association between use of desloratadine and risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter: A nordic register-based study', following procedure EMEA/H/C/xxxx/WS/0641

#### 16.2.8. Edoxaban – LIXIANA (CAP) - EMEA/H/C/002629/MEA/005

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Drug utilisation of edoxaban (DUS), study No. DSE-EDO-01-14-EU: edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study

**16.2.9. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/MEA/002.2**

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Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: revised PASS protocol for study GS-EU-236-0141: non-interventional post-authorisation safety study to assess renal risk minimisation measures among Stribild-treated patients and factors associated with the risk of proximal renal tubulopathy, and its reversibility, including event rates

**16.2.10. Estrogens conjugated, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA/002.1**

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 002 [US PASS protocol, study no. B2311060] request for supplementary information (RSI) as adopted in May 2015

**16.2.11. Estrogens conjugated, bazedoxifene – DUAVIVE (CAP) - EMEA/H/C/002314/MEA/003.1**

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 003 [Final protocol for a drug utilisation study (DUS), study no. B2311061] request for supplementary information (RSI) as adopted in May 2015

**16.2.12. Fingolimod – GILENYA (CAP) - EMEA/H/C/002202/ANX 011.7**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to ANX 011.6 [protocol for a new prospective cohort study assessing the incidence of cardiovascular (CV) adverse events in patients starting Gilenya treatment] request for supplementary information (RSI) as adopted in March 2015

**16.2.13. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA/027.3**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: PASS protocol for a study of golimumab in ulcerative colitis (UC) using the Spanish ENEIDA Registry. This study seeks to evaluate whether the use of GLM is associated with risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer (CRC) or high grade dysplasia (HGD)), and hepatosplenic T cell lymphoma (HSTCL) in patients with UC as compared with alternative therapies for similar severity of disease

16.2.14. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) -  
EMA/H/C/002617/MEA/006.2

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Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 006.1 [first annual report- observational prospective cohort study MI-MA194] request for supplementary information (RSI) as adopted in June 2015

16.2.15. Insulin lispro – LIPROLOG (CAP) - EMA/H/C/000393/MEA/021.1

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 021 [US surveillance programme] request for supplementary information (RSI) as adopted in June 2015

16.2.16. Insulin lispro – HUMALOG (CAP) - EMA/H/C/000088/MEA/028.1

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 028 [US surveillance programme] request for supplementary information (RSI) as adopted in June 2015

16.2.17. Ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) -  
EMA/H/C/003839/MEA/001.1

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Applicant: AbbVie Ltd.

PRAC Rapporteur: Miguel-Angel Macia

Scope: MAH's responses to MEA 001 [observational. cohort study utilising the hepatitis C therapeutic registry & research network (HCV-TARGET)] request for supplementary information (RSI) as adopted in April 2015

16.2.18. Saxagliptin – ONGLYZA (CAP) - EMA/H/C/001039/MEA/033.2  
saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) -  
EMA/H/C/002059/MEA/010.2

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for PASS study CV181-099ST: comparison of risk of major cardiovascular events between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

16.2.19. Saxagliptin – ONGLYZA (CAP) - EMA/H/C/001039/MEA/034.2  
saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) -  
EMA/H/C/002059/MEA/011.2

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for PASS study CV181-100ST: comparison of risk of hospitalisation with acute liver failure between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

**16.2.20. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA/035.2  
saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) -  
EMEA/H/C/002059/MEA/014.2**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for PASS study CV181-103ST: comparison of risk of hospitalisation for severe hypersensitivity (including severe cutaneous reactions) between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

**16.2.21. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA/036.2  
saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) -  
EMEA/H/C/002059/MEA/012.2**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for PASS study CV181-101ST: comparison of risk of hospitalisation with infection between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

**16.2.22. Saxagliptin – ONGLYZA (CAP) - EMEA/H/C/001039/MEA/037.2  
Saxagliptin, metformin hydrochloride – KOMBOGLYZE (CAP) -  
EMEA/H/C/002059/MEA/013.2**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Revised protocol for PASS study CV181-157ST: comparison of risk of hospitalisation for acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral anti-diabetic treatments

**16.3. Results of PASS imposed in the marketing authorisation(s)<sup>38</sup>**

None

**16.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>39</sup>**

**16.4.1. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/II/0015 (with RMP)**

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Applicant: Gilead Sciences International Ltd

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<sup>38</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>39</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013



PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report to investigate the safety and efficacy of GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic HCV post liver transplant (GS-US-334-0126). This submission of this study fulfils MEA 005. An updated RMP (version 3.0) is proposed accordingly.

## **16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>40</sup>**

### **16.5.1. Certolizumab pegol – CIMZIA (CAP) - EMEA/H/C/001037/MEA 005.2**

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Applicant: UCB Pharma SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of interim reports from ARTIS (RA0021), RABBIT (RA0020), US National Databank for Rheumatic Diseases (RA0005) and BSRBR (RA0022)

### **16.5.2. Filgrastim – FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006; ZARZIO (CAP) - EMEA/H/C/000917/MEA 006**

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Applicant: Sandoz GmbH

PRAC Rapporteur: Julie Williams

Scope: Year 3 interim safety report on study EP006: safety follow-up of severe chronic neutropenia (SCN) patients included in phase IV study: safety data will be collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually

### **16.5.3. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 005.4**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual report on a German registry study RABBIT: long-term observational study of the safety of biologic treatments in rheumatoid arthritis

### **16.5.4. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 006.3**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth annual report on a Swedish database registry: review and analysis of adverse events from the Swedish national registry system (CNTOART4003): evaluation of the long-term safety of golimumab across a number of indications, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis using Swedish national (whole population) medical and pharmaceutical datasets

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<sup>40</sup> In line with the revised variations regulation for any submission before 4 August 2013

#### 16.5.5. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 007.1

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second report on a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (CNT0148ART4001)

#### 16.5.6. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/MEA 008.2

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second annual report on an i3 drug safety epidemiology study (CNT0148ART4002): golimumab safety and surveillance program using the Optum research database

#### 16.5.7. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/ANX/002.2; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/ANX/003.1; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/ANX/002.2

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: First interim report for PASS study CQVA149A2402: non-interventional study report multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe

#### 16.5.8. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/MEA/003.2; ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/MEA/004.1; XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/ MEA/003.2

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: First interim report for a drug utilisation study CQVA 149A2401: multinational, multi-database drug utilisation study of indacaterol/ glycopyrronium bromide in Europe to determine the proportion of patients who do not meet the criteria specified in the product information and the proportion of patients who have missing information as per RMP or pre-defined high risk treatment conditions

#### 16.5.9. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/004.3

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Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 004.2 [PASS study D2560C00008, first summary safety report] request for supplementary information as adopted in June 2015

## 16.6. Others

- 16.6.1. Umeclidinium bromide – INCRUSE (CAP) - EMEA/H/C/002809 /LEG/001.1  
Umeclidinium bromide, vilanterol – ANORO (CAP) - EMEA/H/C/002751 /LEG/001.1;  
LAVENTAIR (CAP) - EMEA/H/C/003754 /LEG/001.1
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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to ANX-001 [PASS protocol study 201038: non-interventional post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in COPD patients with UMEC/VI compared with tiotropium as adopted in March 2015: The MAH is requested to submit a copy of the electronic case report form (eCRF) that accurately represents the protocol of the study

## 17. 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.

### 17.1. Annual reassessments of the marketing authorisation

- 17.1.1. Clofarabine – EVOLTRA (CAP) - EMEA/H/C/000613/S/0048 (without RMP)
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Applicant: Genzyme Europe BV

PRAC Rapporteur: Corinne Fechant

Scope: Annual reassessment of the marketing authorisation

- 17.1.2. Galsulfase – NAGLAZYME (CAP) - EMEA/H/C/000640/S/0060 (without RMP)
- 

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

- 17.1.3. Lomitapide – LOJUXTA (CAP) - EMEA/H/C/002578/S/0020 (without RMP)
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Applicant: Aegerion Pharmaceuticals Limited

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

#### 17.1.4. Modified vaccinia Ankara virus – IMVANEX (CAP) - EMEA/H/C/0002596/S/0017 (without RMP)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

#### 17.1.5. Nelarabine – ATRIANCE (CAP) - EMEA/H/C/000752/S/0031 (without RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: Annual reassessment of the marketing authorisation

### 17.2. Conditional renewals of the marketing authorisation

#### 17.2.1. Ex vivo expanded autologous human corneal epithelial cells containing stem cells – HOLOCLAR (CAP) - EMEA/H/C/002450/R/00001 (without RMP)

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

## 18. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 5 – 8 October 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	Full involvement
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No restrictions applicable to this meeting	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No restrictions applicable to this meeting	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Leonidas Klironomos	Member	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Hrefna Guðmundsdóttir	Alternate	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Alternate	Latvia	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
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member - via telephone	Poland	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Alternate - via telephone	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani	Expert - via telephone*	Belgium	No interests declared	Full involvement
Nele Maenhaut	Expert - via telephone*	Belgium	No interests declared	Full involvement
Fabrice Moore	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume	Expert - via telephone*	Belgium	No interests declared	Full involvement
Mikko Jokisalo	Expert - via telephone*	Finland	No interests declared	Full involvement
Sami Paaskoski	Expert - via telephone*	Finland	No interests declared	Full involvement
Sara Miranda	Expert - via telephone*	France	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
Daniel Vittecoq	SAG HIV chair - via telephone*	France	No interests declared	Full involvement
Christine Diesinger	Expert - via telephone*	Germany	No interests declared	Full involvement
Wilma Fischer-Barth	Expert - via telephone*	Germany	No interests declared	Full involvement
Jutta Krappweis	Expert - via telephone*	Germany	No interests declared	Full involvement
Elmer Schabel	Expert - in person*	Germany	No interests declared	Full involvement
Dörte Schwabe	Expert - via telephone*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Zane Stade	Expert - in person*	Latvia	No interests declared	Full involvement
Else Carrière	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Louise Claessen	Expert - in person*	Netherlands	No interests declared	Full involvement
Quirine Fillekes	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Sara Khosrovani	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Stephany Suoth	Expert - via telephone*	Netherlands	No restrictions applicable to this meeting	Full involvement
Polona Golmajer	Expert - via telephone*	Slovenia	No interests declared	Full involvement
Eva Cantarero	Expert - in person*	Spain	No interests declared	Full involvement
Eva Segovia	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Charlotta Bergquist	Expert - via telephone*	Sweden	No interests declared	Full involvement
Rolf Gedeberg	Expert - in person*	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
Olle Karlström	Expert - via telephone*	Sweden	No interests declared	Full involvement
Karolina Törneke	Expert - via telephone*	Sweden	No interests declared	Full involvement
Anna Vikerfors	Expert - in person*	Sweden	No interests declared	Full involvement
Vidar Wendel-Hansen	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Phillip Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Emma Cornforth	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Katherine Donegan	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Dervla Quinn	Expert - in person*	United Kingdom	No interests declared	Full involvement
Suzie Seabroke	Expert - in person*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
<i>For CMDh:</i> Ad hoc experts* and 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.

## 19. 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](#)

## 20. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

### **Risk Management Plans (RMPs)**

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

### **Assessment of Periodic Safety Update Reports (PSURs)**

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

### **Post-authorisation Safety Studies (PASS)**

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

## **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website: [www.ema.europa.eu/](http://www.ema.europa.eu/)