



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

28 January 2021  
EMA/PRAC/87359/2021  
Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC minutes on 23 - 26 November 2020

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

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

### Note on access to documents

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



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## 1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of revision 2 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.2](#)). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

### 1.2. Agenda of the meeting on 23 – 26 November 2020

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

### 1.3. Minutes of the previous meeting on 26 - 29 October 2020

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

Post-meeting note: the PRAC minutes of the meeting held on 26 – 29 October 2020 were published on the EMA website on 08 January 2021 ([EMA/PRAC/12790/2021](#)).

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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

## 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

None

### 3.3. Procedures for finalisation

None

### 3.4. Re-examination procedures<sup>1</sup>

None

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>2</sup>

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

See Annex I 14.1.

### 4.2. New signals detected from other sources

#### 4.2.1. Methotrexate – JYLAMVO (CAP), NORDIMET (CAP); NAP

Applicant(s): Nordic Group B.V. (Nordimet), Therakind (Europe) Limited (Jylamvo); various

PRAC Rapporteur: Martin Huber

Scope: Signal of progressive multifocal leukoencephalopathy

EPITT 18473 – Related to January 2016

Lead Member State(s): AT, DE

#### **Background**

<sup>1</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>2</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

Methotrexate is an antineoplastic and immuno-modulating agent and folic acid analogue. Jylamvo and Nordimet (methotrexate) are centrally authorised products indicated for the treatment of active rheumatoid arthritis in adult patients, polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) and of severe, treatment-refractory, disabling psoriasis which does not respond sufficiently to other forms of treatment, subject to certain conditions. In addition, Jylamvo (methotrexate) is indicated as maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.

Methotrexate has first been authorised in the 1950s. The exposure for methotrexate is estimated to have been more than 12.9 million patient-years worldwide, in the period from 2002 to 2019.

During routine signal detection activities, a signal of progressive multifocal leukoencephalopathy (PML) was identified by EMA<sup>3</sup>, based on one case identified in a literature article by *Simopoulou T et al*<sup>4</sup>. In total, 6 cases were retrieved from EudraVigilance with methotrexate as only suspect drug including 3 cases of level 1 diagnostic certainty<sup>5</sup>. Germany confirmed that the signal needed further analysis and prioritisation by the PRAC.

## Discussion

Having considered the available evidence from the published literature and EudraVigilance on the cases of PML, the PRAC agreed that the MAHs of methotrexate-containing products should provide a cumulative review of cases of PML.

### Summary of recommendation(s)

- The MAHs for methotrexate-containing products with at least one case of PML in their database should submit to EMA, within 60 days, a cumulative review of the signal, including information from post-marketing cases, clinical trials, mechanistic studies and literature. A proposal to amend the product information and RMP should be included as appropriate.
- 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. Capecitabine – CAPECITABINE ACCORD (CAP), CAPECITABINE MEDAC (CAP), CAPECITABINE TEVA (CAP), ECANSYA (CAP), XELODA (CAP) - EMEA/H/C/000316/SDA/036; NAP

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Applicant(s): Accord Healthcare S.L.U. (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine Medac), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva); various

PRAC Rapporteur: Martin Huber

Scope: Signal of anaphylactic reaction

<sup>3</sup> Signal previously assessed in 2015/2016 that recommended further monitoring via routine pharmacovigilance at the time

<sup>4</sup> Simopoulou T, et al. Progressive multifocal leukoencephalopathy in a patient with systemic sclerosis treated with methotrexate: a case report and literature review. *Journal of Scleroderma and Related Disorders*. 2020

<sup>5</sup> Segec, A, Keller-Stanislawski, B, Vermeer, N, Macchiarulo, C, Straus, S, Hidalgo-Simon, A and De Bruin, M (2015), Strategy in Regulatory Decision-Making for Management of Progressive Multifocal Leukoencephalopathy. *Clin. Pharmacol. Ther.*, 98: 502-505. <https://doi.org/10.1002/cpt.199>

EPITT 19561 – Follow-up to June 2020

### **Background**

For background information, see [PRAC minutes June 2020](#).

The MAH for Xeloda (capecitabine) replied to the request for information on the signal of anaphylactic reaction and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from the literature and EudraVigilance, and the cumulative review provided by the MAH, the PRAC agreed that the product information of capecitabine-containing products should be updated to include angioedema as an undesirable effect. In addition, the PRAC considered that a causal relationship between treatment with capecitabine and the occurrence of anaphylactic reactions could not be confirmed in light of the current evidence. Therefore, the PRAC agreed that no update of the product information is warranted at this stage with regard to anaphylactic reactions.

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

- The MAHs for capecitabine-containing products should submit to EMA or to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend<sup>6</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/630091/2020](#) published on 6 January 2021 on the EMA website.

## **4.3.2. Chloroquine (NAP); hydroxychloroquine (NAP)**

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Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of psychiatric disorders

EPITT 19572 – Follow-up to September 2020

### **Background**

For background information, see [PRAC minutes September 2020](#)<sup>7</sup>.

The MAHs for the originator chloroquine- and hydroxychloroquine-containing products replied to the request for information on the signal of psychiatric disorders and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from the updated cumulative reviews provided by the MAHs, the PRAC agreed that additional information on the risk of psychiatric side effects associated with chloroquine/hydroxychloroquine administration should be added to the product information. Therefore, the PRAC agreed that an update of product information is warranted in order to complete the description on psychiatric side effects and to strengthen the recommendations for healthcare professionals (HCPs) and patients.

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<sup>6</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly

<sup>7</sup> Held 31 August–03 September 2020



### Summary of recommendation(s)

- The MAHs for chloroquine and hydroxychloroquine-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend<sup>8</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/630091/2020](#) published on 6 January 2021 on the EMA website.

#### 4.3.3. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/00328/SDA/028

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of vasculitis

EPITT 19578 – Follow-up to September 2020

### Background

For background information, see [PRAC minutes September 2020](#)<sup>9</sup>.

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

### Discussion

Having considered the available evidence on cases of vasculitis from EudraVigilance and from the literature, the PRAC agreed that there is sufficient evidence to establish a causal relationship between pembrolizumab and vasculitis. Therefore, the PRAC agreed that an update of the product information is warranted to add vasculitis as an undesirable effect with a frequency 'rare' when Keytruda (pembrolizumab) is used in monotherapy and 'uncommon' when given in combination with chemotherapy. In addition, a warning on the occurrence of vasculitis should be added.

### Summary of recommendation(s)

- The MAH for Keytruda (pembrolizumab) should submit to EMA, within 60 days, a variation to amend<sup>10</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/630091/2020](#) published on 6 January 2021 on the EMA website.

#### 4.3.4. Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/SDA/052.1, QUTAVINA (CAP), LIVOGIVA (CAP), MOVYMIA (CAP) - EMEA/H/C/004368/SDA/002.1; TERROSA (CAP) - EMEA/H/C/003916/SDA/002.1; NAP

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Applicant(s): Eli Lilly Nederland B.V. (Forsteo), EuroGenerics Holdings B.V. (Qutavina), Gedeon Richter Plc. (Terrosa), Stada Arzneimittel AG (Movymia), Theramex Ireland Limited (Livogiva); various

PRAC Rapporteur: Adrien Inoubli

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<sup>8</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

<sup>9</sup> Held 31 August–03 September 2020

<sup>10</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

Scope: Signal of myeloma

EPITT 19511 – Follow-up to July 2020

### **Background**

For background information, see [PRAC minutes July 2020](#).

The MAHs for Forsteo, Movymia and Terrosa (teriparatide) replied to the request for information on the signal of myeloma and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from EudraVigilance and the literature review provided by the MAHs, the PRAC considered there is insufficient evidence at present to reasonably conclude that teriparatide therapy does induce/promote monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM). Therefore, the PRAC concluded that no regulatory action is warranted at this stage.

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

- The MAHs for teriparatide-containing products should continue to monitor the literature regarding a potential relation between parathyroid hormone in general, including teriparatide therapy, and MM/MGUS.
- In the next PSUR<sup>11</sup>, the MAH of Forsteo (teriparatide) should include details of the protocol and results of the study performed in the IBM MarketScan database as referred to by the MAH in the signal procedure.

For the full PRAC recommendation, see [EMA/PRAC/630091/2020](#) published on 6 January 2021 on the EMA website.

## **4.4. Variation procedure(s) resulting from signal evaluation**

None

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

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

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

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

See also Annex I 15.1.

#### **5.1.1. Berotralstat - EMEA/H/C/005138, Orphan**

Applicant: BioCryst Ireland Limited

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<sup>11</sup> Data lock point (DLP): 12/09/2021

Scope: Prevention of hereditary angioedema (HAE)

### 5.1.2. Cenobamate - EMEA/H/C/005377

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Scope: Adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products

### 5.1.3. COVID-19 mRNA<sup>12</sup> vaccine (nucleoside-modified) – EMEA/H/C/005735

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Scope: Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus)

At an extraordinary meeting convened remotely on 18 December 2020, the PRAC reviewed the proposed RMP in the context of an initial marketing authorisation application procedure. The PRAC is responsible for providing advice to the CHMP.

### 5.1.4. Evinacumab - EMEA/H/C/005449

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Scope (accelerated assessment): Treatment of homozygous familial hypercholesterolemia (HoFH)

### 5.1.5. Pitolisant - EMEA/H/C/005117

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Scope: Treatment of excessive daytime sleepiness (EDS) in patients with obstructive sleep apnoea (OSA)

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

See also Annex I 15.2.

### 5.2.1. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1844/0039; FORXIGA (CAP) - EMEA/H/C/002322/WS1844/0057

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Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Re-categorisation of study D169C00011: a retrospective cohort study on the risk of diabetic ketoacidosis (DKA) to determine the effectiveness of additional risk minimisation measures (aRMMs) in place for DKA by assessing the impact of the risk minimisation measures (RMMs) on the risk of DKA in type 1 diabetes mellitus (T1DM) patients who are treated with dapagliflozin in Europe, from a category 1 to a category 3 study in the RMP (version 20). Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly

#### Background

Dapagliflozin is a sodium glucose co-transporter-2 (SGLT2) indicated, as Edistride and Forxiga, in adults for the treatment of insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise either as monotherapy when metformin is

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<sup>12</sup> Messenger ribonucleic acid

considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of T2DM as well as for the treatment of symptomatic chronic heart failure with reduced ejection fraction. It is also indicated, as Forxiga, in adults for the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin in patients with a body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup>, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

The PRAC is evaluating a worksharing variation for Edistride and Forxiga, centrally authorised products containing dapagliflozin, assessing a request to re-categorise study D169C00011: a retrospective cohort study on the risk of diabetic ketoacidosis (DKA) to determine the effectiveness of additional risk minimisation measures (aRMMs) in place for DKA by assessing the impact of the risk minimisation measures (RMMs) on the risk of DKA in T1DM patients who are treated with dapagliflozin in Europe, from a category 1 to a category 3 study in the RMP. The PRAC is responsible for providing advice to the CHMP on the requested updates to the RMP to support this variation. For further background, see [PRAC minutes July 2020](#) and [PRAC minutes October 2020](#)<sup>13</sup>.

### Summary of advice

- The RMP for Edistride and Forxiga (dapagliflozin) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 20.2 is submitted.
- The PRAC noted the new MAH's proposal for an enhanced passive surveillance (EPS) to rapidly detect significant increases in frequency and/or severity of DKA in EU T1DM patients taking dapagliflozin 5 mg, associated with the DKA PASS re-classified from a category 1 study to a category 3. However, the PRAC considered that it is unclear how the implementation of an EPS would justify the DKA imposed PASS re-classification at this stage. The EPS could potentially give some information of the incidence of DKA but there would be no comparison with patients not taking dapagliflozin 5 mg. Therefore, results would be difficult to be interpreted, and it would not serve the same purpose. It would not provide responses to the same questions as the DKA imposed PASS nor provide data which would be used for the benefit/risk balance assessment such as the data from the imposed DKA PASS. In addition, the PRAC did not consider there was a sufficient scientific basis to support a re-classification of the DKA imposed PASS at this stage. In order to assess the effectiveness of implemented (additional) risk minimisation measures (RMM) introduced at the time of the extension of indication in T1DM, the DKA imposed PASS is expected to be critical for the use of the medicinal product(s) in clinical practice and is hence key to the benefit-risk balance in the T1DM population. The PRAC concurred that the classification of the DKA PASS as an imposed category 1 study should remain unchanged.

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

See Annex I 15.3.

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<sup>13</sup> Held 28 September–01 October 2020

## 6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

#### 6.1.1. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) - NIMENRIX (CAP) - PSUSA/00010044/202004

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

#### Background

Meningococcal group A, C, W135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) is a *Neisseria meningitidis* serogroup B bivalent recombinant lipoprotein indicated, as Nimenrix, for active immunisation of individuals from the age of 6 weeks against invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W-135, and Y.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nimenrix, a centrally authorised medicine containing meningococcal group A, C, W135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein) and issued a recommendation on its marketing authorisation.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Nimenrix (meningococcal group A, C, W135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein)) in the approved indication remains unchanged.
- Nevertheless, the product information should be updated to include lymphadenopathy as an undesirable effect with a frequency 'unknown'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSUR, the MAH should provide detailed reviews of cases of febrile convulsions and cases of urticaria, including a discussion on 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.

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

See also Annex I 16.2.

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<sup>14</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

### 6.2.1. Bortezomib - BORTEZOMIB ACCORD (CAP), BORTEZOMIB FRESENIUS KABI (CAP), BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP), VELCADE (CAP); NAP - PSUSA/00000424/202004

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Applicant(s): Accord Healthcare S.L.U. (Bortezomib Accord), Fresenius Kabi Deutschland GmbH (Bortezomib Fresenius Kabi), Janssen-Cilag International NV (Velcade), Pfizer Europe MA EEIG (Bortezomib Hospira), Sun Pharmaceutical Industries Europe B.V. (Bortezomib Sun), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### **Background**

Bortezomib is a proteasome inhibitor indicated as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma (MM) who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. It is also indicated in combination with melphalan and prednisone for the treatment of adult patients with previously untreated MM who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Additionally, it is indicated in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Finally, it is indicated in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Bortezomib Accord, Bortezomib Fresenius Kabi, Bortezomib Hospira, Bortezomib Sun and Velcade, centrally authorised medicines containing bortezomib, and nationally authorised medicine(s) containing bortezomib and issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of bortezomib-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include Guillain-Barré syndrome (GBS) and demyelinating polyneuropathy as undesirable effects with a frequency 'rare'. Therefore, the current terms of the marketing authorisations should be varied<sup>15</sup>.
- In the next PSUR, the MAHs should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), including a causality assessment by using the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system for diagnosis together with a proposal to update the product information as warranted.

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<sup>15</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

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

#### 6.2.2. Mycophenolate mofetil - CELLCEPT (CAP), MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP); NAP; mycophenolic acid (NAP) - PSUSA/00010550/202005

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Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (CellCept), Teva B.V. (Mycophenolate mofetil Teva, Myfenax), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

##### **Background**

Mycophenolate mofetil (MMF) and mycophenolate acid (MPA), a prodrug of MMF, are immunosuppressive agents indicated for the prevention of acute transplant rejection in patients who have received allogeneic renal, cardiac or hepatic transplants, in combination with ciclosporin and corticosteroids under certain conditions.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of Cellcept, Myclausen and Mycophenolate mofetil Teva and Myfenax, centrally authorised medicines containing mycophenolate mofetil as well as of nationally authorised medicines containing mycophenolate mofetil and nationally authorised medicines containing mycophenolic acid. The PRAC issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mycophenolate mofetil- and mycophenolic acid-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add de novo purine synthesis inhibitors-associated acute inflammatory syndrome as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisations should be varied<sup>16</sup>.
- In the next PSUR, the MAHs should provide cumulative reviews of cases of severe cutaneous adverse reactions and of cases of reversible cerebral vasoconstrictive syndrome (RCVS), addressing all cases of RCVS and cerebral vasoconstriction. The MAHs should also include a discussion for each review on the need to update the product information as 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.

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<sup>16</sup> Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion



### 6.2.3. Somatropin - NUTROPINAQ (CAP), OMNITROPE (CAP); NAP - PSUSA/00002772/202003

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Applicant(s): Ipsen Pharma (NutropinAq), Sandoz GmbH (Omnitrope), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **Background**

Somatropin is a recombinant deoxyribonucleic acid (DNA)-derived human growth hormone indicated for the treatment of growth hormone deficiency (GHD), growth and body composition disturbances associated with Prader-Willi syndrome, growth disturbance in short children/adolescents born small for gestational age, and growth disturbance associated with Turner syndrome, chronic renal insufficiency, idiopathic short stature, and with short stature homeobox-containing gene deficiency.

Based on the assessment of the PSURs, the PRAC reviewed the benefit-risk balance of NutropinAq and Omnitrope, centrally authorised medicines containing somatropin, and nationally authorised medicines containing somatropin and issued a recommendation on their marketing authorisations.

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of somatropin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on pancreatitis and to add gynecomastia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>17</sup>.
- In the next PSUR, the MAHs should provide the rationale for the inclusion/exclusion of headache in their product information as an undesirable effect and include relevant background data.

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

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

See also Annex I 16.1.

#### 6.3.1. Clarithromycin (NAP) - PSUSA/00000788/202004

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Applicant(s): various

PRAC Lead: Ronan Grimes

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<sup>17</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

Scope: Evaluation of a PSUSA procedure

## Background

Clarithromycin is a macrolide indicated for the treatment of infections due to susceptible organisms in adults and children over 6 months including lower and upper respiratory tract infections, skin and soft tissue infections, mycobacterial infections including treatment of mycobacterium avium complex in human immunodeficiency virus (HIV) infected patients. It is also used for treatment of odontogenic infections and for the eradication of *Helicobacter pylori* infection.

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

## Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of clarithromycin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to reflect the potential for interaction between clarithromycin and the direct acting oral anti-coagulants (DOACs) apixaban, dabigatran and rivaroxaban, to advise that caution should be exercised when clarithromycin is co-administered with these agents particularly in patients at high-risk for bleeding, in alignment with the product information of these DOACs. In addition, the product information should be updated to add the concomitant use of clarithromycin with lomitapide as a contraindication. The existing contraindication in patients with hypokalaemia should be modified to reflect that clarithromycin should not be given to patients with either hypokalaemia or hypomagnesaemia, as both types of electrolyte disturbance increase the risk of QT prolongation. Finally, observational study data on the risk of miscarriage and the risk of major congenital malformations and information on the extent of clarithromycin exposure through breast milk should be added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the MAHs should provide a review of cases of blurred vision and visual impairment and discuss whether an update to the product information is warranted. Also, the MAHs should discuss any available data from clinical and non-clinical studies on the transfer of clarithromycin into breast-milk and all available data on the development of adverse effects in infants following exposure to clarithromycin through breastfeeding, including a discussion whether further updates of the product information are warranted. Furthermore, the MAHs should continue to monitor the risk of QT prolongation and torsade de pointe (TdP) in patients with electrolyte disturbances through routine pharmacovigilance and provide a review of any new data/publications.
- In future PSURs, all MAHs should provide a review of post-authorisation use in special patient populations as well as a review of medication errors.

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>18</sup> Update of SmPC sections 4.3, 4.4, 4.5 and 4.6. 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. Deoxycholic acid (NAP) - PSUSA/00010525/202004

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Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### **Background**

Deoxycholic acid is an endogenous bile acid indicated for the treatment of moderate to severe convexity or fullness associated with submental fat (SMF) in adults, subject to certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of deoxycholic acid-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on consequences of inappropriate injection techniques by including scarring as an injection site reaction and to add injection site scarring as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</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.

### 6.3.3. Gentamicin<sup>20</sup> (NAP) - PSUSA/00009159/202003

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Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gentamicin is a broad-spectrum antibiotic of the aminoglycoside group indicated for the treatment of renal and urinary tract infections, respiratory tract infections, intra-abdominal infections, central nervous system infections, bacteraemia, septicaemia, severe neonatal infections, as well as skin, bones, subcutaneous tissue and burn infections.

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

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

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<sup>19</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

<sup>20</sup> Systemic use only

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gentamicin-containing medicinal product(s) 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 provide an overview of their 'summary of safety concerns' and should monitor potential association with gentamicin and necrotising enterocolitis (NEC) in low birth weight infants, as well as the off-label use of gentamicin by intratympanic administration. The MAH Novartis should closely monitor cases of Pseudo-Bartter syndrome and macular ischaemia.

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. Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202003

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

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

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

- The PRAC received feedback from the ad-hoc expert group (AHEG) meeting held on 11 November 2020.
- Based on the review of the data on safety and efficacy, taking into account the responses provided by the authors *Futier et al.* of the FLASH study<sup>21</sup> and the MAHs in writing and in an oral explanation, the PRAC adopted by majority a recommendation concluding that the benefit-risk balance of HES-containing medicinal product(s) in the approved indication(s) remains unchanged.

Twenty-seven members voted in favour of the recommendation whilst six members<sup>22</sup> had divergent views. The Icelandic PRAC member supported the majority, while the Norwegian PRAC member expressed a divergent view.

- The current terms of the marketing authorisation(s) should be maintained.

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<sup>21</sup> Fluid loading in abdominal surgery: saline versus hydroxyethyl starch: a double-blinded multicentre prospective randomised trial

<sup>22</sup> Amelia Cupelli, Ana Sofia Martins, Zane Neikena, Adam Przybylkowski, Anette Kirstine Stark, Ulla Wändel Liminga

- The MAHs should submit to the relevant National Competent Authorities by March 2021 progress reports for the imposed studies PHOENICS<sup>23</sup> and TETHYS<sup>24</sup>.
- In the next PSUR, the MAHs should provide a detailed review of the meta-analysis referred to during the oral explanation, as well as the progress reports for studies PHOENICS and TETHYS.

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. Piroxicam (NAP) - PSUSA/00002438/202004

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **Background**

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) indicated for symptomatic relief of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis as systemic formulations. The topical formulations are indicated for the treatment of painful and inflammatory conditions of rheumatic and traumatic nature of joints, muscles, tendons and ligaments. The topical eye drop formulation is indicated for the treatment of eye inflammatory conditions especially when characterised by pain, possibly of non-infective origin. It is also indicated in case of oedema of the cornea and of the conjunctiva, ocular trauma, uveitis, scleritis, before and after surgery on cataract, corneal neovascularisation on inflammatory basis due to contact lenses.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of piroxicam-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include fixed drug eruption (FDE) as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>25</sup>.
- In the next PSUR, the MAHs should provide a review of cases of eosinophilic pneumonia, including a discussion on the need to update the product information as warranted.

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<sup>23</sup> A prospective, randomized, controlled, double-blind, multicentre, multinational study on the safety and efficacy of a 6% hydroxyethyl starch solution versus an electrolyte solution in patients undergoing elective abdominal surgery

<sup>24</sup> A pragmatic, prospective, randomized, controlled, double-blind, multi-centre, multinational study on the safety and efficacy of 6% hydroxyethyl starch solution versus an electrolyte solution in trauma patients

<sup>25</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

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. Pravastatin (NAP) - PSUSA/00002500/202003

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

##### **Background**

Pravastatin is a competitive inhibitor of 3 hydroxy 3 methylglutaryl coenzyme A (HMG-CoA) reductase (statin) indicated for the treatment of hypercholesterolemia, as primary prevention of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as secondary prevention of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris, and for reduction of post transplantation hyperlipidaemia, subject to certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pravastatin-containing medicinal product(s) 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 provide a cumulative review of cases of gynecomastia, including a causality assessment and a discussion on the need to update the product information as warranted. In addition, the MAHs should submit detailed reviews of cases of cataract, herpes zoster and vasculitis, including hypersensitivity vasculitis.

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

#### 6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

##### 6.4.1. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 161

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of cases of abnormal lipid values in clinical studies and literature data on lipid derangements following tumour necrosis factor alfa (TNF $\alpha$ ) inhibitor treatment

in general and infliximab treatment in particular as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010759/201908) adopted in April 2020

### **Background**

Infliximab is a chimeric human-murine monoclonal antibody that binds to both soluble and transmembrane forms of tumour necrosis factor alfa (TNF $\alpha$ ). It is indicated, as Remicade, for the treatment of rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis and psoriasis, subject to certain conditions.

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine, the PRAC requested the MAH to provide a cumulative review of cases of abnormal lipid values in clinical studies as well as literature data on lipid derangements following TNF $\alpha$  inhibitor treatment. For background information, see [PRAC minutes April 2020](#). The responses were assessed by the Rapporteur for further PRAC advice.

### **Summary of advice/conclusion(s)**

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that there is sufficient evidence to support an association between infliximab administration and dyslipidaemia.
- The MAH should submit to EMA, within 60 days, a variation to amend<sup>26</sup> the product information in order to include dyslipidaemia as an undesirable effect with a frequency 'uncommon'.

## **6.5. Variation procedure(s) resulting from PSUSA evaluation**

### **6.5.1. Ceftaroline fosamil - ZINFORO (CAP) - EMEA/H/C/002252/II/0055**

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Maia Uusküla

Scope: Update of sections 4.4 and 5.2 of the SmPC in order to include information on the use of ceftaroline in patients with cystic fibrosis, based on a pooled population pharmacokinetic (pop PK) analysis that included data from cystic fibrosis patients treated with ceftaroline fosamil as requested in the conclusions of LEG 016 adopted in June 2020, initially requested in the conclusions of periodic safety update single assessment (PSUSA) procedure (PSUSA/00010013/201810) adopted in May 2019. The MAH took the opportunity to make minor editorial changes in the product information

### **Background**

Ceftaroline fosamil is an antibacterial agent for systemic use indicated, as Zinforo, for the treatment of complicated skin and soft tissue infections (cSSTI) and community acquired pneumonia (CAP) in adults and children from the age of 2 months.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine, the PRAC requested the MAH to submit further data on use of ceftaroline in patients with cystic fibrosis and pooled population pharmacokinetic (PK) report based on recently published studies, and a variation to update the product information in order to include information about the use in patients with cystic fibrosis. For background

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<sup>26</sup> Update of SmPC section 4.8. The package leaflet is to be updated accordingly



information, see [PRAC minutes May 2019](#) and [PRAC minutes June 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

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

- Based on the available data and the Rapporteur's assessment, the PRAC agreed that the MAH should provide further evidence to support its proposal to deviate from the previously agreed amendments to the product information.
- The MAH should submit to EMA, within 30 days, responses to the request for supplementary information (RSI).

## **6.6. Expedited summary safety reviews<sup>27</sup>**

See Annex I 16.6.

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

## **7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>28</sup>**

### **7.1.1. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSA/J/0056.1**

Applicant(s): Fresenius Kabi (Volulyte, Voluven), B. Braun Melsungen AG (Tetraspan, Venofundin)

PRAC Rapporteur: Adrien Inoubli

Scope: MAHs' response to PSA/J/0056 [amendment to a joint protocol previously agreed in June 2019 for a retrospective, multinational, drug utilisation study (DUS) to assess the non-adherence of physicians in hydroxyethyl starch (HES) accredited hospitals to the approved European product information regarding indication for use, contraindications and posology (dosage) for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures, as required in the outcome of the referral procedure under Article 107i of Directive 2001/83/EC for HES completed in 2018 (EMEA/H/A-107i/1457)] as per the request for supplementary information (RSI) adopted in September 2020

#### **Background**

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

Further to the conclusions of the referral procedures under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1348](#)) and Article 107i of Directive 2001/83/EC ([EMEA/H/A-107i/1376](#)) in 2013 for HES-containing medicines as well as a further referral procedure under Article 107i of Directive 2001/83/EC ([EMEA/H/A-107i/1457](#)) concluded in 2018, MAHs

<sup>27</sup> Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, In addition to the 6-monthly or annual PSURs falling within the pandemic period

<sup>28</sup> In accordance with Article 107n of Directive 2001/83/EC

were required as a condition of the marketing authorisations ([Annex IV](#)) to implement additional risk minimisation measures.

The MAHs Fresenius Kabi Deutschland GmbH and B. Braun Melsungen AG submitted to the EMA a protocol for a joint study entitled: 'a retrospective, multinational, drug utilisation study (DUS) to investigate the routine use of HES-containing infusion solutions in HES-accredited European (EU) hospitals after implementation of a set of risk minimisation measures' for review by the PRAC. A revised draft amended protocol for a joint non-interventional (PASS) version 4.0 was presented for review by the PRAC. For further background, see [PRAC minutes January 2019](#), [PRAC minutes June 2019](#) and [PRAC minutes September 2020](#)<sup>29</sup>.

#### **Endorsement/Refusal of the protocol**

- The PRAC noted that the MAHs endeavoured to take all measures to reach the protocol required sample size and committed to meet the newly set milestones, including the submission of the final study report by February 2021.
- Having considered the amended protocol version 4.0 in accordance with Article 107o of Directive 2001/83/EC, the PRAC endorsed the substantial amendments to the PASS protocol.

### **7.1.2. Pitolisant – WAKIX (CAP) - EMEA/H/C/PSA/S/0060**

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Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Substantial amendment to a protocol previously agreed in September 2016 for a 5-year multicentre, observational PASS to document the utilisation of Wakix (pitolisant) in the treatment of narcolepsy with or without cataplexy and to collect information on its long-term safety when used in routine medical practice

#### **Background**

Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist indicated, as Wakix a centrally authorised medicine, in adults for the treatment of narcolepsy with or without cataplexy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D](#)) a multicentre, observational post-authorisation safety study should be conducted to document the drug utilisation of Wakix (pitolisant) and to collect information on the safety of Wakix (pitolisant) when used in routine medical practice. The MAH submitted a substantial amendment to the previously agreed protocol in 2016 for review by the PRAC. The PRAC is responsible for evaluating the PASS protocol. For further background, see [PRAC minutes September 2016](#)<sup>30</sup>.

#### **Endorsement/Refusal of the protocol**

- Having considered the amended protocol version 3.0 in accordance with Article 107o of Directive 2001/83/EC, the PRAC agreed with the revised milestones. Nevertheless, the MAH should provide clarifications on the new back-up country with its impact on the study sample size and patients repartition by participating country.

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<sup>29</sup> Held 28 September–01 October 2020

<sup>30</sup> Held 30 August–02 September 2016

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

### 7.1.3. Sotagliflozin – ZYNQUISTA (CAP) - EMEA/H/C/PSP/S/0084.3

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Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0084.2 [protocol for an observational retrospective cohort study using existing data sources on the incidence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1DM) treated with sotagliflozin as an adjunct to insulin versus insulin alone, as required in the outcome of the initial opinion/marketing authorisation (EMEA/H/C/004889) finalised in February 2019] as per the request for supplementary information (RSI) adopted in July 2020

#### **Background**

Sotagliflozin is a dual inhibitor of sodium glucose cotransporter type 1 and type 2 (SGLT1 and SGLT2) indicated, as Zynquista a centrally authorised medicine, as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus (T1DM) with a body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup>, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D](#)) a non-interventional cohort PASS should be conducted in order to estimate the incidence of diabetic ketoacidosis (DKA) in T1DM sotagliflozin treated patients to assess the effectiveness of the risk minimisation measures (RMMs) implemented in Europe using existing data sources in European countries where sotagliflozin will be launched for the indication of T1DM. The MAH submitted protocol version 3 as per a further request for supplement information (RSI) adopted in July 2020. The PRAC is responsible for evaluating the PASS protocol. For further background, see [PRAC minutes September 2019](#), [PRAC minutes February 2020](#) and [PRAC minutes July 2020](#).

#### **Endorsement/Refusal of the protocol**

- Having considered the revised protocol version 3 in accordance with Article 107n of Directive 2001/83/EC, the PRAC objected to the draft protocol as the Committee considered that that the design of the study did not fulfil the study objectives at this stage.
- The MAH should further update the study timelines, propose a matching criterion for the primary analysis analysing its potential positive influence on the sample size, comment on the possible changes of the DKA severity definition, include the crude risk estimates, and provide more detailed information on how the individual composite covariates will be defined.
- The MAH should submit to EMA, within 60 days, a revised PASS protocol. A 60 day-assessment timetable will be followed.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>31</sup>

See Annex I 17.2.

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>32</sup>

### 7.3.1. Teicoplanin (NAP) - EMEA/H/N/PSR/S/0025

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Applicant: Sanofi (Targocid)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSR/S/0025 [results for a PASS study: a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12mg/kg twice a day), and comparison with external historical comparator data] as per the request for supplementary information (RSI) adopted in October 2020

#### Background

Teicoplanin is a glycopeptide antibiotic used for parenteral treatment of infections under certain conditions.

Following the conclusion of a referral procedure under Article 30 of Directive 2001/83/EC ([EMEA/H/A-30/1301](#)) in 2013, a PASS was included as an obligation to the marketing authorisation ([Annex IV](#)) in order to evaluate the safety of Targocid (teicoplanin) in adults with Gram-positive infections who are exposed to the higher loading dose of 12 mg/kg twice a day (24 mg/kg/day). In June 2015, the PRAC adopted a protocol for a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data. For further background, see [PRAC minutes April 2014](#), [PRAC minutes September 2014](#), [PRAC minutes June 2015](#) and [PRAC minutes May 2018](#).

The final study report version 1 dated 20 January 2020 was submitted to EMA by the MAH Sanofi on 2 March 2020 including an addendum report version 1 dated 09 June 2020 for a prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day), and comparison with external historical comparator data. The PRAC discussed the final study results together with the MAH's responses to the request for supplementary information (RSI). The PRAC is responsible for evaluating the PASS results and issuing a recommendation. For further background, see [PRAC minutes May 2020](#) and [PRAC minutes October 2020](#)<sup>33</sup>.

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

- Based on the review of the final report of the non-interventional PASS entitled 'prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day [BID]), and comparison with external historical

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<sup>31</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

<sup>32</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>33</sup> Held 28 September–01 October 2020

comparator data', as well as the MAH's responses to the RSIs, the PRAC considered that the benefit-risk balance of medicinal products containing teicoplanin remains unchanged.

- Nevertheless, the product information should be updated in order to add a warning in order to ensure that teicoplanin is not used by intraventricular route of administration, to reflect adjustments to existing recommendations on thrombocytopenia, nephrotoxicity and ototoxicity. In addition, the description of nephrotoxicity from literature reports are to be reflected, as are the results of the concluded imposed PASS. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>34</sup>.
- At the next regulatory opportunity, the MAH should submit to the relevant National Competent Authorities of the EU Member States, a variation to update the RMP indicating that the condition has been fulfilled.
- As a result of the fulfilment of the study, the medicinal product should be removed from the list of medicines under additional monitoring.
- In the next PSUR<sup>35</sup>, the MAHs should re-evaluate all available data regarding the frequency of thrombocytopenia, hepatotoxicities, as well as hearing and balance disorders.

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>36</sup>

See also Annex I 17.4.

### 7.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0079

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study ALGMYC07390: prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions to test the effectiveness of the approved safety information packet (SIP)

#### Background

Alglucosidase alfa is postulated to restore lysosomal acid- $\alpha$  glucosidase (GAA) activity resulting in stabilisation or restoration of cardiac and skeletal muscle function (including respiratory muscles). It is indicated, as Myozyme a centrally authorised product, for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid  $\alpha$ -glucosidase deficiency).

As stated in the RMP of Myozyme (alglucosidase alfa), the MAH conducted a non-imposed non-interventional study ALGMYC07390 to assess the effectiveness of the approved safety information packet (SIP), a risk minimisation measure (RMM) part of the RMP to address the risk of infusion-associated reactions (IARs) and hypersensitivity reactions (IAR) by serving as an educational resource for treating physicians. The Rapporteur assessed the MAH's final

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<sup>34</sup> Update of SmPC sections 4.4, 4.5 and 4.8. Annex II and the package leaflet are updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>35</sup> Data lock point (DLP): 01/11/2021

<sup>36</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 report in addition to the MAH's responses to the second request for supplementary information (RSI). For further background, see [PRAC minutes March 2020](#) and [PRAC minutes July 2020](#).

### Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report was subject to a further RSI before a recommendation could be made.
- The MAH should submit to EMA, within 60 days, detailed information on the current status of the immuno-surveillance programme in each EU Member State, a discussion on the impact of changes to the SIP if any, their possible impact on the surveillance programme and on the benefit-risk of the medicinal product. In addition, the MAH should provide a discussion on the reasons which might explain low immunogenicity testing in clinical practice and based on this the impact on the effectiveness of the SIP.
- In the next PSUR<sup>37</sup>, the MAH should provide a cumulative review on the impact of immunogenicity testing on the safety and efficacy of the medicinal product. Considering the 2020 annual report on the Pompe registry, the MAH should also discuss in which patient populations the immunogenicity testing may be necessary/useful for clinical practice. Based on this discussion, the MAH should propose an update of the product information and additional risk minimisation measures (aRMM) regarding the advice for immunogenicity testing as warranted.

#### 7.4.2. [Edoxaban - LIXIANA \(CAP\) - EMEA/H/C/002629/WS1760/0024; ROTEAS \(CAP\) - EMEA/H/C/004339/WS1760/0011](#)

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Applicant(s): Daiichi Sankyo Europe GmbH (Lixiana), Berlin Chemie AG (Roteas)

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final study report from study ETNA-DUS (listed as a category 3 study in the RMP): edoxaban treatment in routine clinical practice drug utilisation study - a retrospective drug utilisation chart review study to gain insight on how edoxaban is used in real practice, to identify prescription patterns and to measure the effectiveness of the educational programmes

### Background

Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa (FXa) indicated, as Lixiana and Roteas centrally authorised products, in prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf) with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). It is also indicated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.

As stated in the RMPs of Lixiana and Roteas (edoxaban), the MAH conducted a non-imposed non-interventional PASS entitled ETNA-DUS<sup>38</sup>, a retrospective drug utilisation chart review to assess the effectiveness of educational programmes as risk minimisation measures (RMMs) of Lixiana and Roteas (edoxaban). The Rapporteur assessed the MAH's final study report in

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<sup>37</sup> Data lock point (DLP): 28/09/2021

<sup>38</sup> Study DSE-EDO-01-14-EU: The edoxaban treatment in routine clinical practice drug utilisation study

addition to the MAH's responses to the second request for supplementary information (RSI). For further background, see [PRAC minutes January 2020](#) and [PRAC minutes May 2020](#).

#### **Summary of advice**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC agreed that the study results do not allow drawing strong conclusions on the use of edoxaban. However, the PRAC agreed with the MAH's proposal to update the prescriber guide before treatment in order to measure creatinine clearance and body weight and during treatment to ensure that both parameters are regularly checked. Therefore, the PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.
- In the next PSUR<sup>39</sup>, the MAH should provide a cumulative review of medication errors, with a detailed root cause analysis. Based on this review, the MAH should discuss the need for risk minimisation measures. In addition, the MAH should monitor the impact of the revised prescriber guide on physicians' knowledge and clinical practice.

#### **7.4.3. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0113**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study 20160176 (listed as a category 3 study in the RMP): a retrospective cohort study with the time from index date to diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) as a primary outcome

#### **Background**

Pegfilgrastim is a recombinant human granulocyte colony stimulating factor indicated, as Neulasta a centrally authorised medicine, for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

As stated in the RMP of Neulasta (pegfilgrastim), the MAH conducted a non-imposed non-interventional PASS study 20160176: a retrospective cohort study with the time from index date to diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) to assess these risks for Neulasta (pegfilgrastim). The Rapporteur assessed the MAH's final study report together with MAH's responses to the request for supplementary information (RSI). For further background, see [PRAC minutes July 2020](#).

#### **Summary of advice**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, the PRAC agreed with the update of the product information to refine the existing warning on MDS/AML and to update the adverse drug reaction (ADR) table on MDS/AML under 'neoplasms benign, malignant and unspecified'. Therefore, the PRAC considered that the ongoing variation assessing the final study report can be recommended for approval.

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<sup>39</sup> Data lock point (DLP): 21/10/2021



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

See Annex I 17.5.

## **7.6. Others**

See Annex I 17.6.

## **7.7. New Scientific Advice**

None

## **7.8. Ongoing Scientific Advice**

None

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

None

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

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

See also Annex I 18.1.

### **8.1.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0043 (without RMP)**

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

#### **Background**

Lomitapide is a selective inhibitor of microsomal transfer protein (MTP) indicated for the treatment of adult patients with homozygous familial hypercholesterolaemia (HoFH), under specific conditions.

Lojuxta, a centrally authorised product containing lomitapide, was authorised in 2013 under exceptional circumstances. The benefit-risk of Lojuxta (lomitapide) is reviewed on a yearly basis by the CHMP based on the submission and assessment of additional post-authorisation data (i.e. specific obligations). The PRAC is responsible for providing advice to the CHMP on this annual re-assessment with regard to safety and risk management aspects.

#### **Summary of advice**

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data assessed, the PRAC considered that the annual re-

assessment procedure for Lojuxta (lomitapide) could be finalised provided that the MAH undertakes to fulfil the conditions and obligations.

- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- The PRAC did not support the circulation of future DHPC on an annual basis. In the next annual reassessment procedure, the MAH should discuss the impact of the current DHPC on the adherence to the recommendation of the product information and educational materials.

## 8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

## 8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

### 8.3.1. Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/R/0029 (without RMP)

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Applicant: Orchard Therapeutics (Netherlands) BV; ATMP<sup>40</sup>

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

#### Background

Autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence are immunostimulants indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Strimvelis, a centrally authorised medicine containing autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence, was authorised in 2016.

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

#### Summary of advice

- Based on the review of the available pharmacovigilance data for Strimvelis (autologous CD34<sup>+</sup> enriched cell fraction that contains CD34<sup>+</sup> cells transduced with retroviral vector that encodes for the human ADA cDNA sequence) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the

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<sup>40</sup> Advanced therapy medicinal product

marketing authorisation(s) is warranted based on pharmaceutical grounds relating to a recent case of lymphoid T cells leukaemia requiring further assessment.

## **9. Product related pharmacovigilance inspections**

### **9.1. List of planned pharmacovigilance inspections**

#### **9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products**

Scope: Pharmacovigilance inspection programme 2020-2023 (first revision for 2020)

The EMA Secretariat presented to PRAC the proposed list of planned pharmacovigilance inspections for 2020-2023, the first revision having been agreed by the Pharmacovigilance Inspector Working Group ([PhV IWG](#)) and reviewed according to a risk-based approach. This list is subsequently due for adoption at CHMP. PRAC members were invited to provide final comments by 04 December 2020, afterwards the inspection programme first revision is considered endorsed.

Post-meeting note: On 10 December 2020, the CHMP adopted the pharmacovigilance inspection programme 2020-2023, first revision.

### **9.2. Ongoing or concluded pharmacovigilance inspections**

None

### **9.3. Others**

None

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

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

None

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

None

### **10.3. Other requests**

None

### **10.4. Scientific Advice**

None

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

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

None

### 11.2. Other requests

#### 11.2.1. Dinoprostone (NAP) - SE/H/PSUFU/00001104/201909

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Applicant(s): Ferring (Propess), Pfizer (Minprostin, Prepidil, Prostaglandin E2 Pfizer, Prostin E2)

PRAC Lead: Annika Folin

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure on risk minimisation measures to further minimise the risk of uterine hyperstimulation, including serious complications as uterine rupture, foetal and neonatal death and uterine haemorrhage, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001104/201909) concluded in May 2020, on request of Sweden

#### **Background**

Dinoprostone is a prostaglandin of the E series (PGE<sub>2</sub>) indicated for the induction of labour, as an oral formulation. As endocervical and intravaginal formulations, it is indicated for the ripening of an unfavourable cervix when there is a medical or obstetrical need for labour induction, and for induction of labour, for the termination of pregnancy from the twelfth through the twentieth gestational week and evaluation of the uterine contents in the management of missed abortion or intrauterine foetal death up to 28 weeks of gestational age as well as for management of non-metastatic gestational trophoblastic disease. Finally, as a sterile solution for intravenous (IV) or for extra-amniotic use, it is indicated for the induction of labour and for therapeutic termination of pregnancy, missed abortion and hydatidiform mole.

In the context of the evaluation of a PSUR follow-up (PSU FU) procedure on a review of the risk minimisation measures in place and ways to further minimise the risk of uterine hyperstimulation, including serious complications as uterine rupture, foetal and neonatal death and uterine haemorrhage as requested in the assessment of the last PSUR single assessment (PSUSA) procedure, Sweden as the lead Member State (LMS) requested a further PRAC advice on its assessment. For further background, see [PRAC minutes May 2020](#).

#### **Summary of advice**

- Based on the review of the available information and the LMS assessment, the PRAC supported the LMS proposal to request the MAHs to provide further comments on the proposed product information updates and further consider the need for a direct healthcare professional communication (DHPC) as warranted.

Applicant(s): Bayer (Mirena, Jaydess/Flerec/Luadei/Skyla, Kyleena); Gedeon Richter (Levosert)

PRAC Lead: Martin Huber

Scope: Second PRAC consultation on a PSUR follow-up (PSU FU) procedure on a review of cases reporting meningioma together with a causality assessment, biological plausibility and literature analysis, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00001856/201905) concluded in January 2020, following a previous advice adopted in September 2020, on request of Germany

### Background

Levonorgestrel (LNG) is a second-generation progestin (synthetic progesterone) indicated for hormonal contraception, for the treatment of heavy menstrual bleeding and in several EU countries for idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.

In the context of the evaluation of a PSUR follow-up (PSU FU) procedure on a review of cases reporting meningioma, as requested in the assessment of the last PSUR single assessment (PSUSA) procedure, Germany as the lead Member State (LMS) requested a further PRAC advice on its assessment. For further background, see to [PRAC minutes January 2020](#) and [PRAC minutes September 2020](#)<sup>42</sup>.

### Summary of advice

- Based on the review of the available information and the LMS assessment, the PRAC maintained its advice that meningioma should be addressed as an important potential risk in the summary of safety concerns of upcoming PSURs covering levonorgestrel-containing intrauterine devices (LNG-IUDs). However, based on additional data analysed, the PRAC acknowledged that the current evidence is insufficient to justify a precautionary amendment to the product information of LNG-IUDs at present. Moreover, the PRAC noted that the risk of meningioma has already been evaluated for several progestins and considered that a wider class review for all progestins would not provide further insights into the risk of meningioma for individual progestins (including LNG-IUD) acknowledging that this risk cannot be simply extrapolated from one progestin to another. Instead, the PRAC advised to follow up this safety concern within the next PSUR<sup>43</sup> as part of routine pharmacovigilance.

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

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<sup>41</sup> Levonorgestrel intrauterine device (LNG-IUD)

<sup>42</sup> Held 31 August–03 September 2020

<sup>43</sup> Data lock point (DLP): 08/05/2021

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

None

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

### **12.3.1. Infectious disease working party (IDWP): product information update across all medicinal products with indication in human immunodeficiency virus (HIV) - proposal**

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The EMA Secretariat together with the Chair of the Infectious disease working party ([IDWP](#)) presented to PRAC a proposal to update the product information across all medicinal products with an indication in human immunodeficiency virus (HIV) in order to update the risk of HIV transmission following current the clinical practice and patients' claims sent to the EMA. The PRAC supported the initiative. As a next step, the proposal is going to be discussed at CHMP in December 2020 in order to adopt the wording and way forward for implementation.

Post-meeting note: At its December 2020 meeting, the CHMP also supported the proposal to update the product information across all medicinal products with an indication in HIV. The outcome of the consultation with patients and the next steps will be communicated to PRAC/CHMP in due course.

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

### **12.4.1. Coronavirus (COVID-19) pandemic - update**

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The EMA secretariat updated the PRAC on the activities of the [COVID-19 EMA pandemic Task Force](#) (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance. The EMA Secretariat also provided the PRAC with an update on COVID-19-observational research initiatives. In addition, further procedural information was discussed at PRAC on the upcoming extraordinary PRAC meetings to be convened in the context of the initial evaluation of COVID-19 marketing authorisation applications. Moreover, the EMA Secretariat presented proposals on the handling of the timetables for evaluation of the summary monthly reports for COVID-19 vaccines. Further discussion will be held in due course. Finally, the EMA Secretariat provided PRAC with a detailed overview of the ETF activities.

### **12.4.2. Heads of Medicines Agencies (HMA)-EMA joint big data – Big data training signpost**

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The EMA Secretariat presented to PRAC an update on the Big Data training signpost, consisting of a collection of external training courses on Big Data skills that can benefit the EU regulatory Network until the Big Data curriculum is ready which will contain tailor-made and more targeted trainings instead. The PRAC noted the information. PRAC members can send feedback and questions to the Big Data steering group as needed.

Post-meeting note: On 03 February 2021, a survey on Big Data skills in the EU Regulatory Network was circulated to PRAC members for response by 05 March 2021.

## 12.5. Cooperation with International Regulators

None

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

### 12.6.1. Coronavirus (COVID-19)-vaccines monitoring: ACCESS<sup>44</sup> consortium project - safety and effectiveness - protocols

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PRAC lead: John Joseph Borg, Jean Michel Dogné, Adrien Inoubli, Brigitte Keller-Stanislawski

As one of the EMA initiatives for [real-world monitoring of treatments for COVID-19](#), the EMA secretariat together with the ACCESS ('vACCine Covid-19 monitoring readinESS') coordinators presented to PRAC an update on the progress of the ACCESS project focussing on preparatory research into secondary healthcare data sources and pharmacoepidemiological methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in real-world settings. Research using epidemiological methods on real-world data will provide additional information from clinical practice to complement data collected pre-authorisation through clinical trials and post-authorisation through the EU's regular safety-monitoring activities. The ACCESS project includes at this stage generic protocols for use by MAHs for the monitoring of the safety and effectiveness of their vaccines once they are launched on the market. The PRAC requested clarifications on different aspects of the scope and governance of the project. Further updates will be planned in due course.

### 12.6.2. Coronavirus (COVID-19)-medicines monitoring: CONSIGN<sup>45</sup> consortium project – COVID-19 infection and medicines in pregnancy – protocol

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PRAC lead: Sabine Straus, Ulla Wändel Liminga

As a follow-up to the September 2020 discussion (for background, see [PRAC minutes September 2020](#)<sup>46</sup>), the EMA secretariat together with the CONSIGN ('COVID-19 infectiOn aNd medicineS In preGNancy') coordinators further updated the PRAC on the progress of the CONSIGN project and shared some details on the CONSIGN work package 1 protocol on the multinational registry-based study on COVID-19 infection and medicines in pregnancy based on 9 electronic health databases across 8 EU Member States. Further updates will be planned in due course.

## 12.7. PRAC work plan

### 12.7.1. PRAC work plan 2021 – preparation

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PRAC lead: Sabine Straus, Martin Huber

The EMA secretariat provided an overview of planned topics to be included in the PRAC work plan 2021 based on the experience in 2020 and in light of the current coronavirus (COVID-19

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<sup>44</sup> vACCine Covid-19 monitoring readinESS

<sup>45</sup> Covid-19 infectiOn aNd medicineS In pregnancy

<sup>46</sup> Held 31 August–03 September 2020

outbreak) and the associated EMA business continuity plan (BCP). Further discussion is planned in January 2021.

## **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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PRAC Lead: Menno van der Elst, Maia Uusküla

None

### **12.10.3. PSURs repository**

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None

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

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The PRAC endorsed the draft revised EURD list, version December 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of December 2020, the updated EURD list was adopted by the CHMP and CMDh at their December 2020 meetings and published on the EMA website on 16/12/2020, see:



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

## **12.11. Signal management**

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

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PRAC Lead: Menno van der Elst

The PRAC was updated on the progress from the signal management review technical (SMART) working group meeting held remotely on 05 November 2020. The SMART working group (WG) discussed responses received from the non-urgent information (NUI) recently circulated to the EU regulatory Network on pharmacovigilance initiatives at national levels including information on vaccines monitoring preparedness and vaccination coverage data collection. The WG also discussed proposals for electronic reaction monitoring reports (eRMR) enhancements to visualise coronavirus (COVID-19) cases based on discussion at the SMART workstream on Methods. Finally, the WG considered ways to improve efficiency during the signal management process. Further update will be planned in due course.

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

### **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

### **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 the EMA website on 16/12/2020, see: [Home](#)>[Human Regulatory](#)>[Post-authorisation](#)>[Pharmacovigilance](#)>[Medicines under additional monitoring](#)>[List of medicines under additional monitoring](#)

## **12.13. EudraVigilance database**

### **12.13.1. EudraVigilance – Expert Working Group (EV-EWG) – nomination of PRAC representative**

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As a follow-up to the November 2020 discussion (for background, see [PRAC minutes November 2020](#)<sup>47</sup>), the PRAC endorsed the nomination of Martin Huber to the EudraVigilance Expert Working Group (EV-EWG) as the joint PRAC-EV EWG member. The

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<sup>47</sup> Held 26-29 October 2020

PRAC also agreed with the EV-EWG work programme for 2021-2022.

## **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. Coronavirus (COVID-19)-vaccines – EMA safety updates to the public**

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The EMA Secretariat presented to PRAC plans to publish regular updates on the safety of COVID-19 vaccines once authorised on a dedicated EMA webpage. The EMA Secretariat presented the proposed information elements, the proposed format and proposed frequencies and timing of the safety updates. PRAC members discussed the different proposals and gave their views on consistency with other PRAC documents and synergies with EU Member States communication strategies. Further updates will take place in January 2021.

### **12.18.2. PRAC meeting highlights – proposal for revision**

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As a follow-up to the October 2020 discussion (for background, see [PRAC minutes October 2020](#)<sup>48</sup>) on the extension of the PRAC current format of the PRAC meeting highlights to include information on coronavirus (COVID-19)-related procedures, the EMA Secretariat

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<sup>48</sup> Held 28 September–01 October 2020

presented to PRAC a further proposal for inclusion of additional topics in PRAC highlights as part of a phased approach. In particular, it is planned to include information on procedures for which a direct healthcare professional communication (DHPC) is agreed, for both centrally and nationally authorised medicines. The PRAC agreed with the proposal.

### **12.18.3. Public participation in pharmacovigilance**

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None

### **12.18.4. Safety communication**

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None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

### **12.20.1. Commission implementing Regulation (EU) No 520/2012 – scoping paper**

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The EMA Secretariat informed PRAC of the potential changes to the existing [Commission Implementing Regulation \(EU\) No 520/2012](#) and proposed to initiate some reflection on these changes. EMA has started to work on a scoping paper. In order to consolidate a common proposal, the EMA Secretariat proposed to set up a temporary working group (WG) and to report to PRAC accordingly. A follow-up discussion is planned in March 2021.

Post-meeting note: the following members volunteered to participate in the working group: Sabine Straus, Martin Huber, Menno van der Elst and Ulla Wändel Liminga.

### **12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – update on engagement workstream**

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PRAC lead: Antoine Pariente

On behalf of the PRAC interest group (IG) Impact, the EMA Secretariat provided PRAC with an update on the PRAC impact strategy workstream dedicated to stakeholder engagement (EWS) established in March 2020. As part of its achievements, the PRAC IG worked on conceptualising and defining engagement and outlining how to measure engagement (completed in 2019) and on conducting a case study on the valproate public hearing and dedicated meeting (completed in 2020). As a deliverable, the PRAC IG/EWS plans to develop some points-to-consider for PRAC engagement process in order to guide PRAC on the need for stakeholders' consultation in typical scenarios of safety concerns. The EMA Secretariat presented the plans for 2021 for this deliverable. The PRAC supported the way forward. Further updates will be planned in due course.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>49</sup>

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

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>50</sup>.

#### 14.1.1. Azathioprine (NAP)

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Applicant(s): various

PRAC Rapporteur: Anette Kristine Stark

Scope: Signal of erythema nodosum

EPITT 19623 – New signal

Lead Member State(s): DK

### 14.2. New signals detected from other sources

None

## 15. Annex I – Risk management plans

### 15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

#### 15.1.1. Bevacizumab - EMEA/H/C/005327

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Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

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<sup>49</sup> <sup>49</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>50</sup> Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

#### 15.1.2. Bevacizumab - EMEA/H/C/005611

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Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer; first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer; first line treatment of patients with advanced and/or metastatic renal cell cancer

#### 15.1.3. Dostarlimab - EMEA/H/C/005204

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Scope: Treatment of mismatch repair deficient (dMMR), microsatellite instability-high (MSI-H) endometrial cancer (EC)

#### 15.1.4. Sildenafil - EMEA/H/C/005439

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Scope: Treatment of erectile dysfunction

#### 15.1.5. Thiotepea - EMEA/H/C/005434

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Scope: Conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT), treatment of solid tumours

#### 15.1.6. Trastuzumab - EMEA/H/C/005066

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

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

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

#### 15.2.1. Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0001

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.0) in order to replace the following studies (listed as category 3 studies in the RMP): 1) study CBYL719C2402: a retrospective cohort study to evaluate the risk of hyperglycaemia in patients with advanced breast cancer treated with Piqray (alpelisib) in the real world setting; 2) study CBYL719A0IC02: an open-label, multicentre, phase 3b study to evaluate the safety and tolerability of alpelisib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor-positive (HR+), epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer with a PIK3CA<sup>51</sup> mutation, after disease progression following an endocrine based regimen, with: 3) study CBYL719C2404: A non-interventional PASS of Piqray (alpelisib) in combination with fulvestrant in postmenopausal women, and men, with HR+, HER2 negative, locally advanced or metastatic breast cancer with a PIK3CA mutation

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<sup>51</sup> Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alfa

in the real-world setting in European countries. Additionally, a separated healthcare professional (HCP) survey (CBYL719A0IC02) is proposed as part of the pharmacovigilance plan

#### **15.2.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/II/0027, Orphan**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 3.2) in order to change the final date for completion from July 2020 to May 2024 of the post-authorisation efficacy study (PAES), study 190-203: a phase 2, open-label, multicentre study to evaluate safety, tolerability, and efficacy of intra-cerebroventricular cerliponase alfa in paediatric patients < 18 years of age with neuronal ceroid lipofuscinosis type 2 (CLN2) disease

#### **15.2.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS1972/0049; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS1972/0060**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 6) for Viekirax (ombitasvir/paritaprevir/ritonavir) and Exviera (dasabuvir) in line with the outcome of procedure PSA/J/0055 on direct-acting antiviral (DAAV) concluded in June 2020 relating to a substantial amendment for a joint protocol for a non-interventional imposed PASS on early recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after DAAV therapy, in order to change the due date for submission of the final study report from Q2 2023 to Q3 2021

#### **15.2.4. Ioflupane (<sup>123</sup>I) - DATSCAN (CAP) - EMEA/H/C/000266/II/0060**

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Applicant: GE Healthcare B.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the first RMP (version 0.1) following the introduction of a significant change to the marketing authorisation(s)

#### **15.2.5. Pioglitazone - PIOGLITAZONE ACCORD (CAP) - EMEA/H/C/002277/II/0020**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 5.0) for the removal of safety concerns and additional risk minimisation measures (aRMM) in line with the RMP of Glidipion (pioglitazone) and in line with revision 2 of GVP module V on 'Risk management systems'

#### **15.2.6. Trastuzumab - ONTRUZANT (CAP) - EMEA/H/C/004323/II/0026**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 4.0) in order to propose the early termination of study SB3-G31-BC-E: a long-term follow-up study for cardiac safety in patients with epidermal growth factor receptor 2 (HER2) positive early or locally advanced breast cancer who have completed study SB3-G31-BC (a phase 3 randomised, double-blind, parallel group, multicentre study to compare the efficacy, safety, pharmacokinetics and immunogenicity between Ontruzant (biosimilar trastuzumab) and Herceptin (trastuzumab) in women with newly diagnosed HER2 positive early or locally advanced breast cancer in neoadjuvant setting)

#### 15.2.7. [Travoprost - IZBA \(CAP\) - EMEA/H/C/002738/WS1944/0014; TRAVATAN \(CAP\) - EMEA/H/C/000390/WS1944/0064](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 10.0) for Travatan and Izba (travoprost) in order to remove some important identified risks, important potential risks in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00003011/201902) adopted in November 2019 and in line with revision 2 of GVP module V on 'Risk management systems'

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

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

#### 15.3.1. [Andexanet alfa - ONDEXXYA \(CAP\) - EMEA/H/C/004108/II/0009/G](#)

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Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of an update of section 5.2 of the SmPC in order to update pharmacokinetic (PK) information based on the clinical study results (CSR) from: 1) study 19-514 evaluating the PK comparability of generation 1 process 3 andexanet and generation 2 andexanet (PK comparability); 2) study 16-508: a phase 2 randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability and PK/pharmacodynamics (PD) of andexanet alfa administered to healthy Japanese and Caucasian subjects (Japanese ethnicity study). Annex II-D on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation' is updated accordingly. The RMP (version 2.1) is updated in accordance

#### 15.3.2. [Atazanavir, cobicistat - EVOTAZ \(CAP\) - EMEA/H/C/003904/II/0038](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Extension of indication to include the use of Evotaz (atazanavir/cobicistat) in combination with other antiretroviral agents in the treatment of human immunodeficiency virus 1 (HIV-1) infection in adolescent patients aged  $\geq 12$  to  $< 18$  years, weighing  $\geq 35$  kg

without known mutations associated with resistance to atazanavir. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated in accordance. In addition, the MAH took the opportunity to make minor editorial corrections

### **15.3.3. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0042**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) in combination with platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 14.0) are updated accordingly

### **15.3.4. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/II/0018**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include treatment as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 2.3) are updated in accordance. The MAH took the opportunity to include some editorial changes throughout the product information

### **15.3.5. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0012**

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Extension application to add a new pharmaceutical form (inhalation powder) associated with a new strength (88µg/5µg/9µg). The RMP (version 6.2) is updated in accordance

### **15.3.6. Cabozantinib - CABOMETYX (CAP) - EMEA/H/C/004163/II/0017**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with nivolumab first line treatment of advanced renal cell carcinoma. 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 (version 5.0) are updated in accordance

### **15.3.7. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/II/0011**

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Applicant: Regeneron Ireland Designated Activity Company (DAC)



PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication as monotherapy to include the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing programmed death-ligand 1 (PD-L1) (in  $\geq 50\%$  tumour cells), with no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or proto-oncogene tyrosine-protein kinase ROS1 aberrations, who have locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or have progressed after treatment with definitive chemoradiation, or metastatic NSCLC. The package leaflet and the RMP (version 2.0) are updated accordingly

#### [15.3.8. Cemiplimab - LIBTAYO \(CAP\) - EMEA/H/C/004844/II/0012](#)

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Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication as monotherapy to include the treatment of adult patients with locally advanced basal cell carcinoma (BCC) previously treated with a Hedgehog pathway inhibitor. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated accordingly

#### [15.3.9. Ceritinib - ZYKADIA \(CAP\) - EMEA/H/C/003819/II/0034](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect the results of study CLDK378A2112: a multicentre, randomized open label study to assess the systemic exposure, efficacy and safety of 450 mg ceritinib taken with a low-fat meal and 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in adult patients with anaplastic lymphoma kinase (ALK) rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC). The package leaflet and the RMP (version 16.0) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1). The MAH also introduced other editorial changes including information on sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and the removal of the black triangle

#### [15.3.10. Clopidogrel - ISCOVER \(CAP\) - EMEA/H/C/000175/WS1769/0140; PLAVIX \(CAP\) - EMEA/H/C/000174/WS1769/0138](#)

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include adult patients with high risk transient ischemic attack (TIA) (ABCD<sup>2</sup> score  $\geq 4$ ) or minor ischemic stroke (IS) (National Institutes of Health Stroke Scale (NIHSS)  $\leq 3$ ) within 24 hours of either the TIA or IS event. The new indication is based on the results of: 1) study POINT: a double-blind, randomised, placebo-controlled phase 3 study on platelet-oriented inhibition in new TIA and minor IS; 2) study CHANCE: a

double-blind, randomised, placebo-controlled phase 3 study comparing the effects of a 3-month clopidogrel regimen, combined with acetylsalicylic acid (ASA) during the first 21 days, versus ASA alone for the acute treatment of TIA or minor stroke. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly

#### **15.3.11. Dacomitinib - VIZIMPRO (CAP) - EMEA/H/C/004779/II/0003/G**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations to update sections 4.2 and 5.2 of the SmPC in order to revise the dosing recommendation for patients with hepatic impairment and to include relevant pharmacokinetics data based on results of study A7471058: a phase 1, open-label, single-dose, parallel-group study to evaluate the plasma pharmacokinetics and safety of dacomitinib in participants with severely impaired hepatic function relative to participants with normal hepatic function. As a consequence, the MAH proposed to remove 'safety in patient with severe hepatic impairment' as missing information from the list of safety concerns in the RMP. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1). The MAH took also the opportunity to update the RMP to include study A7471064: a single arm study to evaluate the safety of dacomitinib for the first-line treatment of participants in India with metastatic non-small-cell lung carcinoma (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations as a category 3 study. The RMP (version 1.1) is updated accordingly

#### **15.3.12. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/X/0046/G, Orphan**

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form (dispersible tablets) associated with a new strength (25 mg); 2) extension of indication to include the treatment of children of at least 10 kg of body weight for Delyba (delamanid) 50 mg film-coated tablets. As a consequence, sections 3, 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet, labelling and the RMP (version 3.3) are updated accordingly

#### **15.3.13. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0049**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.7, 4.8, 5.1, 5.2 and 6.6 of the SmPC in order to update efficacy and safety information based on final results from study MDV3100-14 (PROSPER) (listed as a post-authorisation efficacy study (PAES) in Annex II): a phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with non-metastatic castration-resistant prostate cancer. The package leaflet, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 14.0) are updated accordingly. In addition, the MAH took the

opportunity to update the list of local representatives in the package leaflet, to introduce a few editorial updates and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.14. Eravacycline - XERAVA (CAP) - EMEA/H/C/004237/X/0009

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Applicant: Tetrphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension application to add a new strength of 100 mg for eravacycline powder for concentrate for solution for infusion. The RMP (version 3.0) is updated in accordance. Additionally, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

#### 15.3.15. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/II/0001/G

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) extension of indication to include a new indication for the rapid reduction of depressive symptoms in adult patients with a moderate to severe depressive episode of major depressive disorder (MDD) who have current suicidal ideation with intent. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC are updated. The package leaflet and the RMP (version 2.1) are updated accordingly; 2) addition of a new pack size (multipack) of 24 nasal spray devices (multipack of 8 packs of 3 nasal spray devices) corresponding to 4 weeks of treatment in the new indication. The package leaflet and labelling are updated in accordance. In addition, the MAH took the opportunity to clarify the wording in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

#### 15.3.16. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/II/0037

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Update sections 4.4 and 5.1 of the SmPC following the final results from study ZOSTER-064 (listed as a category 3 study in the RMP): an observational study to assess frailty and other prognostic factors for development of herpes zoster in adult subjects who participated in study ZOSTER-006 (study 110390: a phase 3, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older) and ZOSTER-022 (study 113077: a phase 3, randomised, observer blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety and immunogenicity of Shingrix (herpes zoster vaccine) when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older) and the herpes zoster (HZ) efficacy, immunogenicity and safety of Shingrix (herpes zoster vaccine) by frailty status (in fulfilment of MEA 012). The RMP (version 4.1) is updated accordingly. The MAH took the opportunity to implement some editorial changes in sections 4.4 and 5.1 of the SmPC and to introduce a

correction of the abbreviation CHO cells from Chinese hamster ovarian cells to Chinese hamster ovary cells

#### **15.3.17. [Infliximab - REMSIMA \(CAP\) - EMEA/H/C/002576/II/0095](#)**

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Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 4.2 of the SmPC to add a new posology for the rheumatoid arthritis indication that does not include intravenous (IV) induction doses prior subcutaneous use. The package leaflet and the RMP (version 13.1) are updated accordingly

#### **15.3.18. [Insulin aspart - INSULIN ASPART SANOFI \(CAP\) - EMEA/H/C/005033/X/0003](#)**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Extension application to introduce a new route of administration (intravenous use) for the 10 mL vial presentations only. The RMP (version 1.1) is updated accordingly

#### **15.3.19. [Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1881/0085; nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1881/0091](#)**

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Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) for Opdivo (nivolumab) in combination with Yervoy (ipilimumab). 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 (version 20.0 for Opdivo, version 30.0 for Yervoy) are updated in accordance

#### **15.3.20. [Isatuximab - SARCLISA \(CAP\) - EMEA/H/C/004977/II/0003, Orphan](#)**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to add combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.0) are updated accordingly. The MAH took the opportunity to introduce minor changes in sections 4.9, 6.3 and 6.6 of the SmPC and to update details of the local representatives

#### **15.3.21. [Ivacaftor - KALYDECO \(CAP\) - EMEA/H/C/002494/II/0089, Orphan](#)**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to extend the indication of Kalydeco (ivacaftor) tablets in

combination regimen with Kaftrio (ivacaftor/tezacaftor/elexacaftor) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As a consequence, sections 4.1, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.2) are updated in accordance

#### **15.3.22. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0001, Orphan**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to patients with cystic fibrosis (CF) aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR gene), regardless of the second allele (F/any), based on efficacy data from study 104:a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of elexacaftor (VX-445) combination therapy in subjects with CF who are heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF genotypes). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly

#### **15.3.23. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/II/0030**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report from study TDR14311 (listed as a category 3 study in the RMP): a randomised, double-blind, placebo-controlled, dose escalation, study on safety, pharmacokinetics and pharmacodynamics of lixisenatide in paediatric patients with type 2 diabetes mellitus (T2DM) not adequately controlled with metformin and/or basal insulin (in fulfilment of Article 46 requirements). The RMP (version 6.0) is updated accordingly

#### **15.3.24. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0016**

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Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.0) are updated in accordance. Furthermore, the MAH took the opportunity to update the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and the outcome of the referral procedure for methotrexate-containing products under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1463) finalised in July 2019

#### **15.3.25. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0014, Orphan**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to change posology recommendations and add special warnings and precautions for use in the paediatric population following the occurrence of severe dose limiting toxicities (DLTs) based on findings in study CPKC412A2218 (currently on clinical hold): a phase 2, open-label, single arm study to evaluate the safety, efficacy, and pharmacokinetics of twice daily midostaurin (PKC412) combined with standard chemotherapy and as a single agent post-consolidation therapy in children with untreated FMS-like tyrosine kinase 3 (FLT3)-mutated acute myeloid leukaemia (AML). The package leaflet and the RMP (version 5.0) are updated accordingly. The MAH took the opportunity to introduce minor editorial changes in the product information and to bring it in line with the latest quality review of documents (QRD) template (version 10.1)

#### **15.3.26. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0092**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include Opdivo (nivolumab) in combination with cabozantinib for the first line treatment of advanced renal cell carcinoma. 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 (version 19.0) are updated in accordance

#### **15.3.27. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0020**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 5.3 of the SmPC in order to update information on embryo-foetal and pre- and postnatal development in cynomolgus monkeys based on the final report for study 17-1133 (listed as a category 3 study in the RMP): a study assessing the effects of ocrelizumab on embryo-foetal and pre- and post-natal development when administered once weekly for up to 23-weeks intravenously to pregnant cynomolgus monkeys (in fulfilment of MEA 006). The RMP (version 5.0) is updated accordingly

#### **15.3.28. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0042**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to add myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) to the list of adverse drug reactions with the frequency uncommon, to modify the existing warning on MDS/AML and to update efficacy information based on final results from study SOLO-2 (listed as a post-authorisation efficacy study (PAES) in Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product'): a phase 3 randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA<sup>52</sup> mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy. The package leaflet, Annex II and the RMP

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<sup>52</sup> BReast CAncer gene

(version 21.1) are updated accordingly

#### **15.3.29. Oritavancin - ORBACTIV (CAP) - EMEA/H/C/003785/II/0030**

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study 14-TMC-01 (listed as a category 3 study in the RMP): a surveillance study investigation, part of the global SENTRY antimicrobial surveillance programme platform, to monitor the activity of oritavancin against Gram-positive clinical isolates collected from U.S. and European medical centres (in fulfilment of MEA 003.4). The RMP (version 3.0) is updated accordingly

#### **15.3.30. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0039/G**

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of an extension of indication to include the adjuvant treatment after complete tumour resection in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) patients, based on the results from pivotal study D5164C00001: a phase 3, double blind, randomised, placebo-controlled multicentre study to assess the efficacy and safety of Tagrisso (osimertinib) versus placebo, in patients with EGFR mutation positive stage IB-III A NSCLC, following complete tumour resection with or without adjuvant chemotherapy (ADAURA). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 14.1) are updated accordingly

#### **15.3.31. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/II/0026, Orphan**

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final results of study PAR-C10-008: a long-term open-label study investigating the safety and tolerability of a Natpar (parathyroid hormone) for the treatment of adults with hypoparathyroidism – a clinical extension study (RACE). As a consequence, section 5.1 of the SmPC is updated to reflect 72-month data from the study. The RMP (version 3.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

#### **15.3.32. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0091**

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first-line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults based on the results from study KEYNOTE-177: an international, randomised, open-label phase 3 trial of pembrolizumab versus chemotherapy in MSI-H or dMMR stage IV colorectal carcinoma. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are



updated. The package leaflet and the RMP (version 29.1) are updated in accordance. The MAH took the opportunity to introduce minor correction in section 4.4 of the SmPC on immune related endocrinopathies

#### **15.3.33. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/X/0012**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension application to add a new strength of 150 mg for solution for injection in a pre-filled syringe and pre-filled pen. The RMP (version 2.0) is updated accordingly

#### **15.3.34. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0077**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to add the use of romiplostim in adult patients who have had immune thrombocytopenia (ITP) for  $\leq 12$  months and who have had an insufficient response to corticosteroids or immunoglobulins. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 20.0) are updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

#### **15.3.35. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0023**

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Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.5, 4.6 and 5.2 of the SmPC to add drug-drug interaction (DDI) information with rosuvastatin and oral contraceptives based on the results of study CO-338-095 (listed as a category 3 study in the RMP): a phase 1, open-label, DDI study to determine the effect of rucaparib on the pharmacokinetics of oral rosuvastatin (arm A) and oral contraceptives (ethinylestradiol and levonorgestrel - arm B) in patients with advanced solid tumours. The RMP (version 4.1) is updated accordingly

#### **15.3.36. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0037**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 5.1 of the SmPC in order to update the description of the potential risk of emergence of drug resistance with tedizolid phosphate based on final results from study 'surveillance of tedizolid activity and resistance (STAR)' (listed as a category 3 study in the RMP): a surveillance study established in January 2014 to monitor tedizolid susceptibility activity and emergence of resistance across the US, 11 European Union countries, Russia and Turkey. The RMP (version 6.2) is updated accordingly



### 15.3.37. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0027

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Xeljanz (tofacitinib) 11 mg prolonged-release tablets in order to include the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease modifying antirheumatic drug therapy; as an alternative to the immediate release film-coated tablets. Section 4.2 of the SmPC for Xeljanz (tofacitinib) film-coated tablets is also updated to include switching with the prolonged-release tablet in the treatment of PsA. The package leaflet and the RMP (version 13.1) are updated accordingly

### 15.3.38. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0004

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active psoriatic arthritis (PsA) in adult patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance. The MAH took the opportunity to introduce minor updates to Annex II

### 15.3.39. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0005

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active ankylosing spondylitis in adult patient. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated in accordance. The MAH took the opportunity to introduce minor editorial changes throughout the SmPC and Annex II

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

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

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

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

### **16.1.1. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202004**

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Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.1.2. Axicabtagene ciloleucel - YESCARTA (CAP) - PSUSA/00010703/202004**

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Applicant: Kite Pharma EU B.V., ATMP<sup>53</sup>

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### **16.1.3. Benralizumab - FASENRA (CAP) - PSUSA/00010661/202005**

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

### **16.1.4. Bezlotoxumab - ZINPLAVA (CAP) - PSUSA/00010576/202004**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### **16.1.5. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/202004**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

### **16.1.6. Cerliponase alfa - BRINEURA (CAP) - PSUSA/00010596/202004**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **16.1.7. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202004**

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Applicant: AstraZeneca AB

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<sup>53</sup> Advanced therapy medicinal product

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

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**16.1.8. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - PSUSA/00010834/202005**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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**16.1.9. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202004**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.10. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58<sup>54</sup>) - EMEA/H/W/002320/PSUV/0004**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

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**16.1.11. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202004**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.12. Golimumab - SIMPONI (CAP) - PSUSA/00001560/202004**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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**16.1.13. Insulin glargine - ABASAGLAR (CAP), LANTUS (CAP), SEMGLEE (CAP), TOUJEO (CAP) - PSUSA/00001751/202004**

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Applicant(s): Eli Lilly Nederland B.V. (Abasaglar), Mylan S.A.S (Semglee), Sanofi-Aventis Deutschland GmbH (Lantus, Toujeo)

PRAC Rapporteur: Menno van der Elst

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<sup>54</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

Scope: Evaluation of a PSUSA procedure

**16.1.14. Insulin lispro - HUMALOG (CAP), INSULIN LISPRO SANOFI (CAP), LIPROLOG (CAP), LYUMJEV (CAP) - PSUSA/00001755/202004**

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Applicant: Eli Lilly Nederland B.V. (Humalog, Liprolog, Lyumjev), Sanofi-aventis groupe (Insulin Lispro Sanofi)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

**16.1.15. Irinotecan<sup>55</sup> - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - PSUSA/00010534/202004**

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

**16.1.16. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - PSUSA/00010607/202004**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

**16.1.17. Padeliporfin - TOOKAD (CAP) - PSUSA/00010654/202005**

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Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

**16.1.18. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202004**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

**16.1.19. Parecoxib - DYNASTAT (CAP) - PSUSA/00002314/202003**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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<sup>55</sup> Liposomal formulation(s) only

**16.1.20. Radium (<sup>223</sup>Ra) dichloride - XOFIGO (CAP) - PSUSA/00010132/202005**

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Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

**16.1.21. Ruriotocog alfa pegol - ADYNOVI (CAP) - PSUSA/00010663/202005**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.22. Sotagliflozin - ZYNQUISTA (CAP) - PSUSA/00010766/202004**

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Applicant: Guidehouse Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**16.1.23. Sunitinib - SUTENT (CAP) - PSUSA/00002833/202004**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**16.1.24. Susoctocog alfa - OBIZUR (CAP) - PSUSA/00010458/202005**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.25. Ulipristal<sup>56</sup> - ELLAONE (CAP) - PSUSA/00003074/202005**

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Applicant: Laboratoire HRA Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.26. Vestronidase alfa - MEPSEVII (CAP) - PSUSA/00010709/202005**

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

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<sup>56</sup> Indicated for female emergency contraception only

#### 16.1.27. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202005

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 16.2.1. Amlodipine, telmisartan - TWYNSTA (CAP); NAP - PSUSA/00000180/202004

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Applicant(s): Boehringer Ingelheim International GmbH (Twynsta), various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.2.2. Ertapenem - INVANZ (CAP); NAP - PSUSA/00001256/202003

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

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.2.3. Fesoterodine - TOVIAZ (CAP); desfesoterodine (NAP) - PSUSA/00001387/202004

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Applicant: Pfizer Europe MA EEIG (Toviaz), various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### 16.2.4. Naloxone<sup>57</sup> - NYXOID (CAP); NAP - PSUSA/00010657/202005

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Applicant(s): Mundipharma Corporation (Ireland) Limited (Nyxoid), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

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

#### 16.3.1. Aceclofenac (NAP) - PSUSA/00000022/202003

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

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<sup>57</sup> For use in non-medical setting(s) only

#### 16.3.2. Captopril (NAP) - PSUSA/00000535/202004

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Applicant(s): various

PRAC Lead: Marek Juračka

Scope: Evaluation of a PSUSA procedure

#### 16.3.3. Carvedilol, ivabradine (NAP) - PSUSA/00010586/202004

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.3.4. Doxylamine (NAP) - PSUSA/00001174/202004

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Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.3.5. Estradiol<sup>58</sup> (NAP); estradiol, prednisolone (NAP) - PSUSA/00010441/202004

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Applicant(s): various

PRAC Lead: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

#### 16.3.6. Isotretinoin<sup>59</sup> (NAP) - PSUSA/00010488/202005

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

#### 16.3.7. Ivermectin<sup>60</sup> (NAP) - PSUSA/00010376/202004

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Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### 16.3.8. Lamivudine, tenofovir disoproxil (NAP) - PSUSA/00010751/202003

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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<sup>58</sup> Cream/balm/emulsion for application in female genital area only

<sup>59</sup> Oral formulation(s) only

<sup>60</sup> Topical use only

#### 16.3.9. Phenol (NAP) - PSUSA/00009256/202004

Applicant(s): various

PRAC Lead: John Joseph Borg

Scope: Evaluation of a PSUSA procedure

#### 16.3.10. Pimecrolimus (NAP) - PSUSA/00002411/202003

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### 16.3.11. Piribedil (NAP) - PSUSA/00002436/202003

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### 16.3.12. Porfimer (NAP) - PSUSA/00010332/202004

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### 16.3.13. Racecadotril (NAP) - PSUSA/00002602/202003

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

#### 16.3.14. Reboxetine (NAP) - PSUSA/00002615/202004

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.3.15. Simvastatin (NAP) - PSUSA/00002709/202004

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure



#### 16.3.16. Sodium iodide (<sup>123</sup>I) (NAP) - PSUSA/00002752/202003

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### 16.4. Follow-up to PSUR/PSUSA procedures

#### 16.4.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/LEG 097

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Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Review on autoimmunity and autoantibodies based on data from the study by *Hineno et al.*<sup>61</sup> and the study by *Blitshetyn et al.*<sup>62</sup> as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00009175/201911) adopted in June 2020

#### 16.4.2. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 159

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Review on administration of live vaccines, including a literature review on postnatal clearance of tumour necrosis factor alfa (TNF $\alpha$ ) inhibitors in the newborn, particularly of infliximab and of cases of disseminated BCG<sup>63</sup> vaccinations associated with administration of BCG after birth as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010759/201908) adopted in April 2020

#### 16.4.3. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 160

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Cumulative review of cases of hidradenitis including data from clinical trials, post-marketing experience and literature, and taking into account the intended use (indication or off-label use) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010759/201908) adopted in April 2020

#### 16.4.4. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/LEG 015.1

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Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

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<sup>61</sup> Hineno A, Shu-ichi Ikeda, Scheibenbogen C, Heidecke H, Schulze-Forster K, Junker, et al. Autoantibodies against autonomic nerve receptors in adolescent Japanese girls after immunization with human papillomavirus vaccine. *Ann Arthritis Clin Rheumatol.* 2019;2(2):1014

<sup>62</sup> Blitshetyn S, Brinth L, Hendrickson JE, Martinez-Lavin M. Autonomic dysfunction and human papillomavirus vaccine (HPV) immunization: an overview. *Immunol Res.* 2018;66(6):744-54

<sup>63</sup> Bacillus Calmette-Guerin

Scope: MAH's response to LEG 015 [details on study Truven MarketScan<sup>64</sup> and cumulative review of cases of intestinal perforation as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010025/201908) adopted in March 2020] as per the request for supplementary information (RSI) adopted in July 2020

## **16.5. Variation procedure(s) resulting from PSUSA evaluation**

None

## **16.6. Expedited summary safety reviews<sup>65</sup>**

### **16.6.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.4**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Seventh expedited monthly summary safety report for remdesivir for November 2020 including spontaneously reported data and data from compassionate use and expanded access programmes for the duration of the coronavirus disease (COVID-19) pandemic

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

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

### **17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>66</sup>**

None

### **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>67</sup>**

#### **17.2.1. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.3**

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Substantial amendment to a protocol previously agreed in July 2019 for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings

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<sup>64</sup> Truven MarketScan claims database used to assess the potential association between linaclotide and gastrointestinal (GI) perforation

<sup>65</sup> Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

<sup>66</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>67</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

### 17.2.2. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 002.2

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Substantial amendment to a protocol previously agreed in June 2019 for study BO40853 (listed as a category 3 study in the RMP): a PASS based on healthcare professional (HCP) and patient/carer survey to evaluate awareness, knowledge and compliance of HCPs and patients/carers to additional risk minimisation measures (guide for HCPs, patient/carer guide, patient alert card), in relation to the safety concerns of thromboembolic events, thrombotic microangiopathy and life-threatening bleeding due to misinterpretation of the standard coagulation tests

### 17.2.3. Fostamatinib - TAVLESSE (CAP) - EMEA/H/C/005012/MEA 002.1

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study BIG-CL-PRT-000015: a post-authorisation long term safety surveillance study of fostamatinib in adult patients with chronic immune thrombocytopenia (cITP) who are refractory to previous treatment [final clinical study report (CSR) expected in March 2025]] as per the request for supplementary information (RSI) adopted in July 2020

### 17.2.4. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 002.2

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Substantial amendment to a protocol previously agreed in March 2020 for observational cohort study TV48125-MH-50037: a pregnancy registry assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab)

### 17.2.5. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.1

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006 [protocol for study ALN-AS1-006: a global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP) [ELEVATE]] as per the request for supplementary information (RSI) adopted in July 2020

### 17.2.6. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 009.4

Applicant: Shire Services BVBA

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 009.3 [substantial amendment to a protocol previously agreed in April 2020 for study SHP617-400 (EU AIR): an European multicentre, multi-country, post-authorisation observational study (registry) of patients with chronic adrenal

insufficiency] as per the request for supplementary information (RSI) adopted in September 2020

#### **17.2.7. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 003**

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Applicant: Celgene Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Protocol for a study to evaluate the effectiveness of the additional risk minimisation measures in Europe in order to assess healthcare professionals (HCP) awareness of key messages included in the HCP checklist for luspatercept including recommendations for counselling of women of child bearing potential (WCBP) and instructions for providing WCBP with the patient card (from initial opinion/marketing authorisation(s) (MA))

#### **17.2.8. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 002.1**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 002 [protocol for a study (listed as a category 3 study in the RMP) on pregnancy outcomes intensive monitoring (PRIM) in order to prospectively collect and evaluate safety data on pregnancy outcomes and congenital malformations related to siponimod exposure immediately before and during pregnancy [final clinical study report (CSR) expected in 2030]] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.2.9. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 004.1**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 004 [protocol for a survey study (listed as a category 3 study in the RMP) among healthcare professionals (HCPs) and patients/caregivers in selected European countries in order to evaluate whether HCPs and patients/caregivers receive the educational materials and to capture their knowledge and behaviour around specific siponimod safety measures] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.2.10. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.1**

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Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Julia Pallos

Scope: MAH's response to MEA 002 [protocol for study JZP865-401: a PASS to evaluate the long-term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol] as per the request for supplementary information (RSI) adopted in July 2020

#### 17.2.11. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 030

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Protocol for study F506-PV-0001: a non-interventional PASS on outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI) registry

#### 17.2.12. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 022

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study F506-PV-0001: a non-interventional PASS on outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI) registry

#### 17.2.13. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 014.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 014 [protocol for study A3921321: a drug utilisation study (DUS) on the utilisation and prescribing patterns of Xeljanz (tofacitinib) in two European countries using administrative claims databases and national registries for assessment, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in July 2020

#### 17.2.14. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 003.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 003 [protocol for study P19-150: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in Europe to evaluate the safety of upadacitinib among patients with RA receiving routine clinical care [final study report expected in March 2030]] as per the request for supplementary information (RSI) adopted in June 2020

#### 17.2.15. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 004 [protocol for study P19-141: a long-term post-authorisation safety study (PASS) of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and

serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged  $\geq 75$  years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies [final study report expected in March 2033]] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.2.16. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005.1**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 005 [protocol for study P20-199: a drug utilisation study (DUS) to evaluate the effectiveness of the additional risk minimisation measures (aRMM) in place to describe the baseline characteristics of new users of upadacitinib, and in a similar manner, to describe new users of a biological disease-modifying antirheumatic drugs (bDMARD) for comparison [final study report expected in September 2024]] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.2.17. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.9**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 044.8 [substantial amendment to a protocol previously agreed in October 2019 for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in July 2020

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>68</sup>**

None

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>69</sup>**

#### **17.4.1. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0068**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report related to the physician survey (NO6987) conducted for Exjade (deferasirox) to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations (dispersible tablets and film-coated

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<sup>68</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>69</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

tablets). The RMP (version 17.1) is updated accordingly

#### **17.4.2. [Dulaglutide - TRULICITY \(CAP\) - EMEA/H/C/002825/II/0051](#)**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final study report for study B009 (listed as a category 3 study in the RMP): a multi-database collaborative research programme of observational studies to monitor the drug utilisation and safety of dulaglutide in the EU (in fulfilment of MEA 002). The RMP (version 6.1) is updated accordingly

#### **17.4.3. [Etanercept - ENBREL \(CAP\) - EMEA/H/C/000262/WS1653/0230; LIFMIOR<sup>70</sup> - EMEA/H/C/004167/WS1653/0024](#)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Eva Segovia

Scope: Submission of the second 5-year report from the British Society for Rheumatology Biologics Register (BSRBR) also referred as study B1801309 (listed as a category 3 study in the RMP). This is a prospective observational cohort study which investigates the long-term outcomes of patients with rheumatoid arthritis treated with etanercept with particular reference to safety

#### **17.4.4. [Florbetaben \(<sup>18</sup>F\) - NEURACEQ \(CAP\) - EMEA/H/C/002553/II/0033](#)**

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Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study FBB-01\_03\_13 (PASS-2) (listed as a category 3 study in the RMP): a non-interventional, cross-sectional, retrospective, multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (<sup>18</sup>F)) in European clinical practice. The RMP (version 5.9) is updated accordingly

#### **17.4.5. [Nitisinone - ORFADIN \(CAP\) - EMEA/H/C/000555/II/0074](#)**

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Applicant: Swedish Orphan Biovitrum International AB

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study Sobi.NTBC-005 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the long-term safety of Orfadin (nitisinone) treatment in hereditary tyrosinaemia type 1 (HT-1) patients in standard clinical care. The RMP (version 5.3) is updated accordingly

#### **17.4.6. [Ustekinumab - STELARA \(CAP\) - EMEA/H/C/000958/II/0082](#)**

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Applicant: Janssen-Cilag International NV

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<sup>70</sup> Marketing authorisation(s) ceased to be valid in the European Union (EU) on 16 February 2020

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final safety registry report of study CNTO1275PSO4005 (listed as a category 3 study in the RMP): a Nordic database initiative for exposure to ustekinumab - a review and analysis of adverse events from the Swedish and Danish national registry systems. The RMP (version 18.2) is updated accordingly

#### **17.4.7. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0049, Orphan**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of final physician data study results for study EUPASS 14255: an evaluation of the effectiveness of risk minimisation measures - a survey among healthcare professionals (HCPs) and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alfa (Vpriv) in 6 European countries

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

#### **17.5.1. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.8**

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Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.7 [5-year interim results for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation, in light of available data [final clinical study report (CSR) expected in December 2024]] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.5.2. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.8**

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Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.7 [5-year interim results for study EP06-501 (SMART): a non-interventional, prospective, long-term safety data collection of Zarzio/Filgrastim Hexal (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell (PBPC) mobilisation, in light of available data [final clinical study report (CSR) expected in December 2024]] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.5.3. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/ANX 041.9**

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Applicant: Celgene Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to ANX 041.8 [second interim descriptive report for study CC-5013-



MDS-012 (listed as a category 1 study in Annex II): a post-authorisation, non-interventional, retrospective, drug-utilisation study (DUS) to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)] as per the request for supplementary information (RSI) adopted in June 2020

#### **17.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.8**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Fourth annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice [final clinical study report (CSR) expected in December 2024]

### **17.6. Others**

#### **17.6.1. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/ANX 004.3**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Substantial amendment to a protocol previously agreed by CHMP in September 2017 for study SHP503-401: a phase 4, interventional, multicentre, 2-part study composed of a 1-year randomised, double-blind, parallel-group, placebo-controlled, active-comparator, dose-optimisation evaluation followed by a 1-year open-label evaluation to assess the long-term safety of Intuniv (guanfacine) on selected domains of cognition in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD) for whom stimulants are not suitable, not tolerable, or shown to be ineffective

#### **17.6.2. Radium (<sup>223</sup>Ra) dichloride - XOFIGO (CAP) - EMEA/H/C/002653/MEA 015**

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Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Interim report for study PEACE-3 - European Organisation for Research and Treatment of Cancer (EORTC)-sponsored phase 3 study: a randomised multicentre phase 3 trial comparing enzalutamide vs a combination of radium-223 dichloride and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer (CRPC) patients metastatic to bone in order to address the important identified risk of bone fractures [final clinical study report (CSR) expected in April 2021] as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in 2018 (EMEA/H/A-20/1459)

### **17.7. New Scientific Advice**

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

## 17.8. Ongoing Scientific Advice

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

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

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

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

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

## 18.1. Annual reassessments of the marketing authorisation

### 18.1.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0048 (without RMP)

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

### 18.1.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0028 (without RMP)

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

### 18.1.3. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0064 (with RMP)

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

### 18.1.4. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0017 (without RMP)

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual reassessment of the marketing authorisation

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

### **18.2.1. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/R/0015 (with RMP)**

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Applicant: Portola Netherlands B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### **18.2.2. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/R/0045 (without RMP)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

### **18.2.3. Cabozantinib - COMETRIQ (CAP) - EMEA/H/C/002640/R/0042 (with RMP)**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### **18.2.4. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0047 (without RMP)**

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Conditional renewal of the marketing authorisation

### **18.2.5. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0027 (without RMP)**

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Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

### **18.2.6. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0009 (without RMP)**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

## **18.3. Renewals of the marketing authorisation**

### **18.3.1. Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/R/0024 (without RMP)**

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Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

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**18.3.2. Eftrenonacog alfa - ALPROLIX (CAP) - EMEA/H/C/004142/R/0032 (without RMP)**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

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**18.3.3. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/R/0064 (without RMP)**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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**18.3.4. Lutetium (<sup>177</sup>Lu) chloride - ENDOLUCINBETA (CAP) - EMEA/H/C/003999/R/0019 (without RMP)**

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Applicant: ITM Medical Isotopes GmbH

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

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**18.3.5. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/R/0027 (with RMP)**

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Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

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**18.3.6. Opicapone - ONGENTYS (CAP) - EMEA/H/C/002790/R/0031 (with RMP)**

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Applicant: Bial - Portela & C<sup>a</sup>, S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

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**18.3.7. Palonosetron - PALONOSETRON ACCORD (CAP) - EMEA/H/C/004129/R/0009 (without RMP)**

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

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**18.3.8. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/R/0032 (without RMP)**

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Applicant: Novartis Europharm Limited

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 23-26 November 2020 meeting (marked as "a") and for the 18 December 2020 extraordinary meeting (marked as "b").

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus <sup>a, b</sup>	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser <sup>a, b</sup>	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik <sup>a, b</sup>	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné <sup>a, b</sup>	Member	Belgium	No interests declared	Full involvement
Laurence de Fays <sup>a, b</sup>	Alternate	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva <sup>a, b</sup>	Member	Bulgaria	No interests declared	Full involvement
Julian Eftimov <sup>b</sup>	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce <sup>a, b</sup>	Member	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou <sup>a, b</sup>	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras <sup>a, b</sup>	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová <sup>a, b</sup>	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova <sup>a, b</sup>	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark <sup>a, b</sup>	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted <sup>a, b</sup>	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla <sup>a, b</sup>	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka <sup>a, b</sup>	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola <sup>a, b</sup>	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli <sup>a</sup>	Member	France	No interests declared	Full involvement
Tiphaine Vaillant <sup>a, b</sup>	Alternate	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
Martin Huber <sup>a, b</sup>	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski <sup>a, b</sup>	Alternate	Germany	No interests declared	Full involvement
Agni Kapou <sup>a, b</sup>	Member	Greece	No interests declared	Full involvement
Sofia Trantza <sup>a, b</sup>	Alternate	Greece	No interests declared	Full involvement
Julia Pallos <sup>a, b</sup>	Member	Hungary	No participation in final deliberations and voting on:	6.3.6. Pravastatin (NAP) 15.3.2. Atazanavir, cobicistat - EVOTAZ (CAP) 15.3.19. Ipilimumab - YERVOY (CAP); nivolumab - OPDIVO (CAP) 15.3.26. Nivolumab - OPDIVO (CAP) 17.2.7. Luspatercept - REBLOZYL (CAP) 17.5.3. Lenalidomide - REVLIMID (CAP) 17.5.4. Nivolumab - OPDIVO (CAP)
Melinda Palfi <sup>a, b</sup>	Alternate	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir <sup>a, b</sup>	Member	Iceland	No participation in discussion, final deliberations and voting on:	7.4.3. Pegfilgrastim - NEULASTA (CAP) 15.3.13. Enzalutamide - XTANDI (CAP) 15.3.34. Romiplostim - NPLATE (CAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.2.11. Tacrolimus - ADVAGRAF (CAP); 17.2.12. Tacrolimus - MODIGRAF (CAP)
Rhea Fitzgerald <sup>a, b</sup>	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes <sup>a, b</sup>	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli <sup>a, b</sup>	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli <sup>a, b</sup>	Alternate	Italy	No interests declared	Full involvement
Zane Neikena <sup>a, b</sup>	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene <sup>a, b</sup>	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain <sup>b</sup>	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Anne-Cécile Vuillemin <sup>a, b</sup>	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg <sup>a, b</sup>	Member	Malta	No interests declared	Full involvement
Menno van der Elst <sup>a, b</sup>	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan <sup>a, b</sup>	Alternate	Netherlands	No interests declared	Full involvement
David Olsen <sup>a, b</sup>	Member	Norway	No participation in final deliberations and voting on:	4.3.2. Chloroquine (NAP); hydroxychloroquine (NAP) 11.2.1. Levonorgestrel (NAP); 16.1.20. Radium (223Ra) dichloride - XOFIGO (CAP) 17.6.2. Radium (223Ra) dichloride - XOFIGO (CAP)
Karen Pernille Harg <sup>a, b</sup>	Alternate	Norway	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
Adam Przybylkowski <sup>a, b</sup>	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska <sup>b</sup>	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins <sup>a, b</sup>	Member	Portugal	No interests declared	Full involvement
Marcia Silva <sup>a, b</sup>	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe <sup>b</sup>	Member	Romania	No interests declared	Full involvement
Alexandra-Maria Spurni <sup>a, b</sup>	Alternate	Romania	No interests declared	Full involvement
Michal Radik <sup>a, b</sup>	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka <sup>a, b</sup>	Alternate	Slovakia	No interests declared	Full involvement
Gabriela Jazbec <sup>a, b</sup>	Member	Slovenia	No interests declared	Full involvement
Jasmina Klopčič <sup>b</sup>	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia <sup>a, b</sup>	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon <sup>a, b</sup>	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga <sup>a, b</sup>	Member	Sweden	No interests declared	Full involvement
Annika Folin <sup>a, b</sup>	Alternate	Sweden	No interests declared	Full involvement
Milou Daniel Drici <sup>a, b</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Birgitta Grundmark <sup>a, b</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales <sup>a, b</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng <sup>a, b</sup>	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente <sup>a, b</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Stefan Weiler <sup>a, b</sup>	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson <sup>a, b</sup>	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini <sup>a, b</sup>	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne <sup>a, b</sup>	Member	Patients' Organisation Representative	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
Virginie Hivert <sup>a, b</sup>	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Christelle Bizimungu <sup>b</sup>	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Jamila Hamdani <sup>b</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Fabrice Moore <sup>a</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Martine Sabbe <sup>b</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Françoise Wuillaume <sup>b</sup>	Expert - via telephone*	Belgium	No interests declared	Full involvement
Ivana Ljubičić <sup>a</sup>	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Karin Susanne Erneholm <sup>a, b</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Pernille Gammelgaard <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Astrid Munch Hestbæk <sup>a</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Moritz Sander <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Ane Blicher Schelde <sup>a</sup>	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Bibi Fatima Syed Shah <sup>b</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Sandra Jeanette Wallerek <sup>a</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe <sup>b</sup>	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kroot Aab <sup>a</sup>	Expert - via telephone*	Estonia	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
Alice Aribaud <sup>a</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Alexandre Moreau <sup>b</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Jean-Michel Race <sup>b</sup>	Expert - via telephone*	France	No interests declared	Full involvement
Harald Enzmann <sup>b</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Maxim Frizler <sup>a</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Thomas Grueger <sup>a</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex <sup>a</sup>	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Karin Seifert <sup>a</sup>	Expert - via telephone*	Germany	No interests declared	Full involvement
Orsolya Papp <sup>a</sup>	Expert - via telephone*	Hungary	No interests declared	Full involvement
Grainne Kirwan <sup>a, b</sup>	Expert - via telephone*	Ireland	No interests declared	Full involvement
Oleg Sabelnikovs <sup>a</sup>	Expert - via telephone*	Latvia	No restrictions applicable to this meeting	Full involvement
Martine Trauffler <sup>b</sup>	Expert - via telephone*	Luxembourg	No interests declared	Full involvement
Marcel S.G. Kwa <sup>b</sup>	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Petrus (Pim) Luijsterburg <sup>b</sup>	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Maria Vanenburg <sup>b</sup>	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Ida Bergva Aas <sup>a</sup>	Expert - via telephone*	Norway	No interests declared	Full involvement
Bjorg Bolstad <sup>b</sup>	Expert - via telephone*	Norway	No restrictions applicable to this meeting	Full involvement
Ingrid Wang <sup>b</sup>	Expert - via telephone*	Norway	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
Bruno Sepodes <sup>b</sup>	Expert - via telephone*	Poland	No restrictions applicable to this meeting	Full involvement
Maria Jesus Fernandez Cortizo <sup>a</sup>	Expert - via telephone*	Spain	No interests declared	Full involvement
Helena Back <sup>b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Charlotte Backman <sup>a, b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Helena Faust <sup>b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson <sup>b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Jessica Mwinyi <sup>b</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
Sara Vennberg <sup>a</sup>	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

## 20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

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

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

<https://www.ema.europa.eu/en>