28 February 2022
EMA/PRAC/121854/2022
Human Medicines Division

# Pharmacovigilance Risk Assessment Committee (PRAC)

## Minutes for the meeting on 03-06 May 2021

Chair: Sabine Straus – Vice-Chair: Martin Huber

**Disclaimers**

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

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

**Note on access to documents**

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

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
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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). David Olsen declared an additional competing interest regarding a close family member interest for coronavirus (COVID-19) mRNA[1] vaccine (EMEA/H/C/005845).

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 remotely). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

## 1.2. Agenda of the meeting on 03-06 May 2021

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 06-09 April 2021

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

Post-meeting note: the PRAC minutes of the meeting held on 06-09 April 2021 were published on the EMA website on 10 February 2022 (EMA/PRAC/89475/2022).

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

## 2.1. Newly triggered procedures

None

[1] Messenger ribonucleic acid

## 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[2]

None

## 3.5. Others

None

# 4. Signals assessment and prioritisation[3]

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

See also Annex I 14.1.

### 4.1.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of acute macular outer retinopathy

EPITT 19703 – New signal

Lead Member State(s): BE

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

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

During routine signal detection activities, a signal of acute macular outer retinopathy (AMOR) was identified by EMA based on 10 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC. At the organisational, regulatory and methodological matters (ORGAM)[4] meeting held on 20 May 2021, PRAC discussed the signal and adopted a recommendation.

**Discussion**

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed that further assessment is warranted in view of the consistent time to onset (TTO) across the reported cases and known cases of acute macular neuroretinopathy (AMN) reported after influenza vaccination.

**Summary of recommendation(s)**

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) should submit to EMA, within 30 days, a cumulative review of cases of AMN/AMOR including post-marketing, clinical trials and literature data. The review should include a discussion on a plausible mechanism of action together with a proposal to amend the product information/RMP as warranted.

## 4.2. New signals detected from other sources

None

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/SDA/011

Applicant(s): Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of sarcoidosis

EPITT 19638 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

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

**Discussion**

[4] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

Having considered the available evidence from EudraVigilance, the literature, nonclinical and clinical data, additional data submitted by the MAH together with the Rapporteur's assessment, PRAC considered that there is sufficient evidence to establish a causal association between treatment with alemtuzumab and sarcoidosis. Therefore, PRAC agreed that an update of the product information is warranted to add sarcoidosis as a warning and as an undesirable effect with a frequency uncommon.

**Summary of recommendation(s)**

- The MAH for Lemtrada (alemtuzumab) should submit to EMA, within 60 days, a variation for amending[5] the product information.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.2. Clindamycin (NAP)

Applicant(s): various

PRAC Rapporteur: Sonja Hrabcik

Scope: Signal of acute renal failure

EPITT 19647 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAH of the originator clindamycin-containing product(s) replied to the request for information on the signal of acute renal failure and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence from EudraVigilance, the literature, and additional data submitted by Pfizer, the MAH of the originator clindamycin-containing product(s) together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to establish a causal association between treatment with clindamycin (systemic use) and acute kidney injury. Therefore, PRAC agreed that an update of the product information is warranted to add acute kidney injury as a warning and as an undesirable effect with a frequency not known.

**Summary of recommendation(s)**

- The MAHs for clindamycin-containing products for systemic use should submit to the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to amend[6] the product information.

Post meeting note: At the organisational, regulatory and methodological matters (ORGAM) meeting on 22 July 2021, PRAC adopted a revised recommendation refining the recommended wording.

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

For the full PRAC recommendation, see EMA/PRAC/250777/2021 Corr2 published on 26 August 2021 on the EMA website.

### 4.3.3. Coronavirus (COVID-19) mRNA[7] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/023

Applicant(s): BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of localised swelling in persons with history of dermal filler injections

EPITT 19674 – Follow-up to March 2021

**Background**

For background information, see PRAC minutes March 2021.

The MAH replied to the request for information on the signal of localised swelling in persons with history of dermal filler injections and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence from EudraVigilance and the data submitted by the MAH together with the Rapporteur's assessment, PRAC considered that there is sufficient evidence to establish a causal association between Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) and localised swelling in persons with history of dermal filler injections. Therefore, PRAC agreed that an update of the product information is warranted to add facial swelling as an undesirable effect with a frequency not known.

**Summary of recommendation(s)**

- The MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 14 days, a variation for amending[8] the product information.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.4. Coronavirus (COVID-19) mRNA[9] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/SDA/026

Applicant(s): Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of immune thrombocytopenia

EPITT 19679 – Follow-up to March 2021

**Background**

For background information, see PRAC minutes March 2021.

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

[7] Messenger ribonucleic acid
[8] Update of section 4.8 of the SmPC. The package leaflet is to be updated accordingly
[9] Messenger ribonucleic acid

**Discussion**

Having considered the available evidence from EudraVigilance, the data submitted by the MAH together with the Rapporteur's assessment, PRAC agreed that further information is needed to fully assess the risk of immune thrombocytopenia (ITP) with COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) and to reach a final recommendation.

**Summary of recommendation(s)**

- The MAH for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA, within 30 days, responses to a further request for supplementary information, including an updated observed/expected (O/E) analysis based on the most recent data. The MAH should also discuss the need to update the product information and/or RMP as warranted.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.3.5. Coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant]) - COVID-19 vaccine JANSSEN (CAP) - EMEA/H/C/005737/SDA/018.1

Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of embolic and thrombotic events

EPITT 19689 – Follow-up to April 2021

**Background**

For background information, see PRAC minutes April 2021.

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

**Discussion**

Taking into account data from EudraVigilance, clinical, pre-clinical and literature data, additional data submitted by the MAH and the Rapporteur's assessment, PRAC further reviewed evidence concerning thromboembolic events in association with COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) with a particular focus on cases with combination of thrombosis with thrombocytopenia syndrome (TTS). PRAC agreed that an update of the product information is warranted to include information to outline that patients who are diagnosed with thrombocytopenia within three weeks of vaccination should be actively investigated for signs of thrombosis. Similarly, the product information should reflect that patients who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

**Summary of recommendation(s)**

- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) should submit to EMA, within 1 day, a variation for amending[10] the product information.

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

- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) should submit to EMA, within 14 days, a variation to amend the RMP to add TTS as an important identified risk and thrombocytopenia as an important potential risk. Protocols of existing post-authorisation observational studies should be modified to include the adverse event of special interest (AESI) regarding embolic and thrombotic events.
- The MAH for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])) should submit to EMA, within 90 days, a variation to further amend the RMP by updating the pharmacovigilance plan to further characterise TTS.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.6. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/034

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of immune thrombocytopenia

EPITT 19678 - Follow-up to March 2021

**Background**

For background information, see PRAC minutes March 2021.

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

**Discussion**

PRAC considered the available evidence including the data submitted by the MAH and the Rapporteur's assessment, the fact that thrombocytopenia was added to the product information as an undesirable effect (EPITT 19683 – see PRAC minutes April 2021 and under 4.4.1. ) and the need to further characterise the risk and the additional pharmacovigilance activities proposed by the MAH. PRAC agreed to request further information from the MAH before drawing a final recommendation.

**Summary of recommendation(s)**

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 30 days, a cumulative review of cases on thrombocytopenia without co-reported thromboembolic events from the global safety database and a refined observed/expected (O/E) analysis. In addition, the MAH should include data from clinical trials relating to cases of abnormal platelet level presented in the clinical laboratory evaluation were associated with clinical symptoms and/or reported in subjects with a relevant medical history. In addition, the MAH should provide more information and timelines related to the exploratory analysis and observational studies to further characterise thrombocytopenia.

### 4.3.7. Eliglustat - CERDELGA (CAP) - EMEA/H/C/003724/SDA/016

Applicant(s): Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Signal of erectile dysfunction

EPITT 19644 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

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

**Discussion**

Having considered the available evidence from EudraVigilance, the literature, non-clinical and clinical data, the cumulative review submitted by the MAH together with the Rapporteur's assessment, PRAC agreed that at this stage, there is insufficient evidence to establish a causal association between Cerdelga (eliglustat) and erectile dysfunction in light of the current knowledge.

**Summary of recommendation(s)**

- The MAH for Cerdelga (eliglustat) should continue to monitor cases of erectile dysfunction as part of routine safety surveillance.

## 4.3.8. Immune checkpoint inhibitors: atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/021; avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/SDA/007; cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/SDA/007; durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/SDA/007; ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/SDA/041; pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/029; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/042

Applicant(s): AstraZeneca AB (Imfinzi), Bristol-Myers Squibb Pharma EEIG (Opdivo, Yervoy), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland Designated Activity Company (DAC) (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Menno van der Elst

Scope: Signal of immune-mediated cystitis

EPITT 19610 – Follow-up to November 2020

**Background**

For background information, see PRAC minutes of PRAC minutes November 2020[11].

The MAHs replied to the request for information on the signal of immune-mediated cystitis and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence from EudraVigilance, literature data, as well as the plausible mechanism of action and the data submitted by the MAHs together with the Rapporteur's assessment, PRAC agreed that there is sufficient evidence for a potential class effect of immune-mediated non-infectious cystitis induced by treatment with check point

[11] Held 26-29 October 2020

inhibitors (ICIs). Therefore, PRAC agreed that an update of the product information is warranted to add cystitis non-infective and agreed to consult the MAHs on a proposal for amendment before a final recommendation can be reached.

**Summary of recommendation(s)**

- The MAHs for Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Yervoy (ipilimumab), Keytruda (pembrolizumab) and Opdivo (nivolumab) should submit to EMA, within 30 days, a proposal to amend the product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.9. Labetalol (NAP)

Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of nipple pain and suppressed lactation

EPITT 19639 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAH Aspen Pharma for the originator labetalol-containing product(s) replied to the request for information on the signal of nipple pain and suppressed lactation and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence, including data submitted by MAH Aspen Pharma together with the Rapporteur's assessment, PRAC agreed that further information is needed to fully assess the risk of suppressed lactation, nipple pain with Raynaud's phenomenon and nipple pain alone (without Raynaud's phenomenon) associated with labetalol in order to reach a final recommendation.

**Summary of recommendation(s)**

- The MAH Aspen Pharma should submit to EMA, within 60 days, responses to a further RSI.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.3.10. Methotrexate - JYLAMVO (CAP) - EMEA/H/C/003756/SDA/003, NORDIMET (CAP) - EMEA/H/C/003983/SDA/004; NAP

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

PRAC Rapporteur: Martin Huber

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 18473 – Follow-up to December 2020

**Background**

For background information, see PRAC minutes December 2020[12].

The MAHs replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence from EudraVigilance and the reviews provided by the MAHs together with the Rapporteur's assessment, PRAC agreed that further information is needed in order to fully assess the possible causal association between PML and methotrexate treatment and to reach a final recommendation.

**Summary of recommendation(s)**

- The MAHs should submit to EMA, within 60 days, additional data regarding the risk of PML following methotrexate treatment. The responses should include a review of concomitant or co-suspected medications in reported cases of PML with methotrexate together with a discussion of potentially different frequencies of reported co-medications, taking into account treatment schedules of underlying health conditions and available literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.3.11. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/SDA/006

Applicant(s): UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of cardiac arrhythmia

EPITT 19629 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

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

**Discussion**

Having considered the available evidence from EudraVigilance, the literature, non-clinical and clinical data and additional data submitted by the MAH together with the Rapporteur's assessment, PRAC agreed that at this stage, there is insufficient evidence to establish a causal association between treatment with romosozumab and cardiac arrhythmia. However, while confounding factors were reported in the majority of cases which precluded causality assessment, some events were reported with a close temporal relationship. Furthermore, while an imbalance of major adverse cardiovascular events (MACE) was observed within the

[12] Held 23-26 November 2020

pivotal phase 3 study ARCH[13], the precise aetiology has to be elucidated yet. Therefore, PRAC agreed that the RMP should be updated to include cardiac arrythmias as an important potential risk and to add a targeted follow-up questionnaire (FUQ) related to cardiac arrhythmia. Moreover, PRAC agreed that the protocol for study OP0004 (PASS#2)[14] should be amended to include cardiac arrythmias as specific events. Finally, the MAH should update the list of safety concerns within the PSUR in order to include the risk of cardiac arrhythmias as an important potential risk.

**Summary of recommendation(s)**

- The MAH for Evenity (romosozumab) should submit to EMA, within 90 days, a variation to update the RMP. The protocol for study OP0004 should be also amended.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

## 4.3.12. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/SDA/011

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Signal of Henoch-Schonlein purpura

EPITT 19640 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAH replied to the request for information on the signal of Henoch-Schonlein purpura and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence in EudraVigilance, literature and the cumulative review of vasculitis cases submitted by the MAH as well as the Rapporteur's assessment, PRAC agreed that there is sufficient evidence to establish a causal association between treatment with secukinumab and hypersensitivity vasculitis. Therefore, PRAC agreed that an update of the product information is warranted to add hypersensitivity vasculitis as an undesirable effect with a frequency rare.

**Summary of recommendation(s)**

- The MAH for Cosentyx (secukinumab) should submit to EMA, within 60 days, a variation for amending[15] the product information.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

[13] A multicentre, international, randomized, double-blind, alendronate-controlled study to determine the efficacy and safety of romosozumab in the treatment of postmenopausal women with osteoporosis
[14] European non-interventional PASS related to serious cardiovascular adverse events of myocardial inforaction and stroke for romosozumab by the EU-ADR Alliance
[15] Update of section 4.8 of SmPC. The package leaflet is to be updated accordingly

## 4.3.13. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant(s): various

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of acute respiratory distress syndrome

EPITT 19625 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAHs Roche/Eumedica, Aspen Pharma and Teva as originator and brand leaders for sulfamethoxazole/trimethoprim (co-trimoxazole)-containing products replied to the request for information on the signal of acute respiratory distress syndrome (ARDS) and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence, including the reviews submitted by the MAHs for co-trimoxazole containing medicinal products as well as the Rapporteur's assessment, PRAC agreed that there is a close temporal relationship between sulfamethoxazole/trimethoprim (co-trimoxazole) and ARDS, the extensive negative workup paired with recent co-trimoxazole exposure in some cases, as well as observed similarities between cases suggested co-trimoxazole-induced ARDS. Therefore, PRAC agreed that an update of the product information is warranted to add ARDS as a warning.

**Summary of recommendation(s)**

- The MAHs for sulfamethoxazole/trimethoprim (co-trimoxazole)-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[16] the product information.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

## 4.3.14. Sulfametoxazole, trimethoprim (co-trimoxazole) (NAP)

Applicant(s): various

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of haemophagocytic lymphohistiocytosis (HLH)

EPITT 19655 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAHs Roche/Eumedica, Aspen Pharma and Teva as originator and brand leaders for sulfamethoxazole/trimethoprim (co-trimoxazole)-containing products replied to the request for information on the signal haemophagocytic lymphohistiocytosis (HLH) and the responses were assessed by the Rapporteur.

[16] Update of section 4.4 of the SmPC. The package leaflet is to be updated accordingly. The wording should supersede any existing warning on lung infiltration or respiratory toxicity and corresponding package leaflet text

**Discussion**

Having considered the available evidence in EudraVigilance, the literature, the cumulative reviews submitted by the MAHs as well as the Rapporteur's assessment, PRAC agreed that in view of cases with positive dechallenge, the potential mechanism of action and the seriousness of the condition, that an update of the product information is warranted to add HLH as a warning.

**Summary of recommendation(s)**

- The MAHs for medicinal products containing sulfamethoxazole/trimethoprim in combination should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[17] the product information.
- The MAHs should add HLH as a PSUR important safety concern and monitor any new cases in PSURs.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.15. Tramadol (NAP); tramadol, dexketoprofen (NAP); tramadol, paracetamol (NAP)

Applicant(s): various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of serotonin syndrome

EPITT 19635 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAHs of tramadol-containing products eligible to submit PSURs replied to the request for information on the signal of serotonin syndrome and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence and following the assessment of the data submitted by the concerned MAHs together with the Rapporteur's assessment, PRAC agreed that a causal relationship between tramadol alone in overdose situation and at therapeutic doses and serotonin syndrome is at least a reasonable possibility and a causal relationship between treatment with tramadol and serotonin syndrome cannot be excluded. Therefore, PRAC agreed that an update of the product information is warranted to add serotonin syndrome as a warning, as an undesirable effect and as part of the interaction and overdose sections. PRAC also agreed this recommendation is applicable to fixed-dose combinations containing tramadol.

**Summary of recommendation(s)**

- The MAHs for tramadol containing medicinal products, including fixed combinations of tramadol-paracetamol and tramadol-dexketoprofen should submit to the relevant

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

National Competent Authorities (NCAs) of the Member States, within 60 days, a variation for amending[18] the product information.

For the full PRAC recommendation, see EMA/PRAC/250777/2021 published on 31 May 2021 on the EMA website.

### 4.3.16. Warfarin (NAP)

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of anticoagulant-related nephropathy

EPITT 19652 – Follow-up to January 2021

**Background**

For background information, see PRAC minutes January 2021.

The MAH Bristol-Myers Squibb for the originator warfarin-containing product(s) replied to the request for information on the signal of anticoagulant-related nephropathy and the responses were assessed by the Rapporteur.

**Discussion**

Having considered the available evidence from EudraVigilance, literature and data provided by the MAH Bristol-Myers Squibb as well as the Rapporteur's assessment, PRAC agreed that further data is needed in order to conclude for a possible causal association between warfarin treatment and anticoagulant-related nephropathy and to reach a final recommendation.

**Summary of recommendation(s)**

- The MAH Bristol-Myers Squibb for the originator warfarin-containing product(s) should submit to EMA, within 60 days, responses to a further request for supplementary information (RSI). This includes a clinical evaluation of literature case reports concerning anticoagulant-related nephropathy/warfarin related nephropathy, a further literature search for any available data in which renal function during warfarin treatment is assessed as well as an evaluation of patient groups with increased risk of anticoagulant-related nephropathy or risk factors. The MAH should provide a proposal to update the product information as warranted.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

### 4.4.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/II/0014

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.3, 4.4 and 4.8 of the SmPC, following an update to the

[18] Update of sections 4.4, 4.5, 4.8 and 4.9 of the SmPC. The package leaflet is to be updated accordingly. Any existing wording should be adjusted to the recommended product information changes

company core data sheet (CCDS) in relation to thromboembolism with thrombocytopenia in order to contraindicate the vaccine to patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine, update the warnings on thrombocytopenia and coagulation disorders and include the frequency thrombosis with thrombocytopenia of 'less than 1/100,000'. The package leaflet is updated accordingly. The variation is linked to the signal procedure (EPITT 19683) finalised in April 2021

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

In relation to the evaluation of a signal procedure concluded in April 2021 on embolic and thrombotic events (EPITT 19683), the MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) performed an update to the company core data sheet (CCDS) and submitted to EMA a variation to update the product information with thromboembolism with thrombocytopenia in order to contraindicate the vaccine to patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia under certain condition, update the warnings on thrombocytopenia and coagulation disorders and include the frequency thrombosis with thrombocytopenia. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. For background information, see PRAC minutes April 2021.

**Summary of outcome(s) adopted at the plenary meeting**

- Based on the available data and the Rapporteur's assessment, PRAC agreed to request supplementary information (RSI) to the MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]).
- The MAH should further refine its proposal to update the product information. In addition, the MAH should provide a draft direct healthcare professional communication (DHPC) together with a communication plan in order to inform healthcare professionals on the changes to the product information, on the need for expert consultation for diagnosis and treatment and on the need for a high level of suspicion for thrombosis if thrombocytopenia is diagnosed.

**Background** of the organisational, regulatory and methodological matters (ORGAM)[19] meeting

PRAC assessed the MAH's responses to the RSI adopted on 06 May 2021 at the PRAC plenary meeting and adopted a further outcome at the ORGAM meeting held on 20 May 2021.

**Summary of outcome(s) adopted at the ORGAM meeting**

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's assessment, PRAC supported to update the product information[20] to add a contraindication for individuals who have experienced thrombosis with

[19] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)
[20] Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly

thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]), relevant warning with addition of symptoms for individuals diagnosed with thrombocytopenia or who present thrombosis within three weeks after vaccination with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) together with an update of the existing undesirable effects on thrombocytopenia and thrombosis with thrombocytopenia syndrome.

- PRAC agreed on the content of a further direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

# 5. Risk management plans (RMPs)

## 5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

### 5.1.1. Avalglucosidase alfa – NEXVIADYME - EMEA/H/C/005501, Orphan

Applicant: Genzyme Europe BV

Scope: Long-term enzyme replacement therapy for the treatment of patients with Pompe disease

### 5.1.2. Bamlanivimab - EMEA/H/C/005836

Scope: Treatment of coronavirus (COVID-19)

### 5.1.3. Bevacizumab - EMEA/H/C/005433

Scope: Treatment in adults of neovascular macular degeneration associated with aging and diabetes

### 5.1.4. Coronavirus (COVID-19) mRNA[21] vaccine - EMEA/H/C/005845

Scope: Active immunisation for prevention of coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults ≥18 years old

### 5.1.5. Etesevimab - EMEA/H/C/005837

Scope: Treatment of coronavirus (COVID-19) in combination with bamlanivimab

[21] Messenger ribonucleic acid

### 5.1.6. Tafasitamab - EMEA/H/C/005436, Orphan

Applicant: Incyte Biosciences Distribution B.V.

Scope: Treatment in combination with lenalidomide of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from I low grade lymphoma, who are not eligible for, or refuse, autologous stem cell transplant (ASCT)

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

See also Annex I 15.2.

### 5.2.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/II/0015

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of an updated RMP (version 3.1) in order to update the safety concerns to add 'thrombosis in combination with thrombocytopenia' as an important identified risk and 'thrombosis' as an important potential risk, with consequential changes in the RMP. Updates to the pharmacovigilance plan have also been implemented. These changes are implemented in line with the recommendation of the signal procedure on 'embolic and thrombotic events' (EPITT 19683) adopted in April 2021. The MAH took the opportunity to further update the RMP to reclassify 'anaphylaxis' as an important identified risk, already reflected in the product information as an adverse drug reaction

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

PRAC is evaluating a type II variation procedure for Vaxzevria, a centrally authorised medicine containing COVID-19 vaccine (ChAdOx1-S [recombinant]), to update the RMP to add 'thrombosis in combination with thrombocytopenia' as an important identified risk and 'thrombosis' as an important potential risk in line with the recommendation of the signal procedure on 'embolic and thrombotic events' (EPITT 19683) adopted in April 2021. The MAH took the opportunity to further update the RMP to reclassify 'anaphylaxis' as an important identified risk and to implement further changes throughout the RMP. For further background, see PRAC minutes April 2021.

PRAC is responsible for producing an assessment report to be further considered at the level of CHMP, responsible for adopting an opinion on this variation. At the organisational, regulatory and methodological matters (ORGAM)[22] meeting on 20 May 2021, PRAC adopted its outcome.

**Summary of advice**

[22] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

- The RMP for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in the context of the variation procedure under evaluation by PRAC could be considered acceptable provided that an update to RMP version 3.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should reword the identified risk of 'thrombosis in combination with thrombocytopenia' to 'thrombosis with thrombocytopenia syndrome' according to the recent interim case definition of the Brighton Collaboration. Regarding the pharmacovigilance plan, the MAH should include further measurements to the study on in vitro expression of S-protein (listed as a category 1 study) in order to confirm whether the protein is adequately folded and if any accumulation of the translated protein is localised in the endoplasmic reticulum and/or cytoplasm, leading to unfolded protein response (UPR) in the cell. Regarding heparin-induced thrombocytopenia antibodies in vaccinated sera, the inclusion of sera from vaccinated individuals that displayed thrombosis and/or thrombocytopenia and individuals that did not display such event should be included as control in the relevant studies. For ongoing and planned clinical trials, the MAH should consider actively investigating for signs of thrombosis if thrombocytopenia is diagnosed in vaccinated subjects. In completed clinical trials, the MAH should confirm that all samples with negative results for anti-platelet factor 4 (PF4) antibodies were collected prior to administration of any treatment and they were analysed by an ELISA[23] test. Clarifications on the selection criteria of samples to be sent for functional analysis should be provided.

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

See also Annex I 15.3.

### 5.3.1. Coronavirus (COVID-19) mRNA[24] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/II/0030

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication from 'individuals 16 years of age and older' to 'individuals 12 years of age and older'. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 2.0) are updated in accordance

**Background**

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 16 years and older.

CHMP is evaluating an extension of the therapeutic indication for Comirnaty, a centrally authorised product containing COVID-19 mRNA vaccine (nucleoside-modified), to include individuals of 12 years of age and older. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. At the organisational, regulatory and methodological matters (ORGAM)[25] meeting on 20 May 2021, PRAC adopted its outcome.

[23] Enzyme Linked ImmunoSorbent Assay
[24] Messenger ribonucleic acid
[25] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

**Summary of advice**

- The RMP for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) in the context of the variation under evaluation by CHMP could be considered acceptable provided that an update to RMP version 2.0 is submitted.
- The MAH should confirm that adolescents of 12-15 years will be included in each of the post-authorisation studies stated in the pharmacovigilance plan and comment on the envisaged paediatric sample size for each post-authorisation study as applicable. The MAH should also comment on the progress of studies and update the pharmacovigilance plan accordingly. The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

### 5.3.2. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0043, Orphan

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include treatment of adult patients with systemic light chain (AL) amyloidosis. 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 8.2) are updated in accordance

**Background**

Daratumumab is an immunoglobulin G (IgG)1κ human monoclonal antibody indicated, as Darzalex, for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. It is also indicated in combination with lenalidomide, dexamethasone, bortezomib, melphalan, prednisone, thalidomide and lenalidomide, under certain conditions.

CHMP is evaluating an extension of the therapeutic indication for Darzalex, a centrally authorised product containing daratumumab, to include the treatment of adult patients with systemic light chain (AL) amyloidosis. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes February 2021.

**Summary of advice**

- The RMP version 8.3 for Darzalex (daratumumab) in the context of the extension of indication variation under evaluation by CHMP is considered acceptable.
- The MAH should submit to EMA, within 90 days of the CHMP opinion, the study protocol for the proposed PASS[26] to further characterise cardiac adverse events. The MAH should discuss what percentage of patients will have pre-existing severe cardiac involvement at baseline and whether the study is powered enough to characterise the risk. The MAH should also discuss in detail the feasibility of the proposed study.

[26] A multicentre prospective study to further characterise cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management and outcome

### 5.3.3. Padeliporfin - TOOKAD (CAP) - EMEA/H/C/004182/II/0013

Applicant: Steba Biotech S.A

PRAC Rapporteur: Maia Uusküla

Scope: Extension of indication to modify the wording of the existing indication to treatment of adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and clinical stage T1c or T2a, International Society of Urological Pathology (ISUP) grade group ≤ 2, based on high-resolution biopsy strategies, prostate-specific antigen (PSA) ≤ 10 ng/mL, low core positivity. As a consequence, section 4.1 of the SmPC is updated. The RMP (version 6.0) is updated accordingly

**Background**

Padeliporfin is a sensitizer used in photodynamic/radiation therapy indicated, as Tookad, a centrally authorised product, for adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years, under certain conditions.

CHMP is evaluating an extension of the therapeutic indication for Tookad, a centrally authorised product containing padeliporfin, to modify the wording of the existing indication to treatment of adult patients with previously untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years and clinical stage T1c or T2a, International Society of Urological Pathology (ISUP) grade group ≤ 2, based on high-resolution biopsy strategies, prostate-specific antigen (PSA) ≤ 10 ng/mL, low core positivity. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation.

**Summary of advice**

- The RMP for Tookad (padeliporfin) in the context of the of the variation under evaluation by CHMP could be considered acceptable provided that an update to RMP version 6.0 is submitted.
- PRAC supported the removal of study CLIN1501 PCM401[27] being a post-authorisation efficacy study (listed as a category 1 study). The amendments of the study protocol should be assessed separately from the ongoing procedure.

# 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. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202009

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

[27] Long-term observational cohort study of patients with unilateral low risk localised prostate cancer treated with Tookad vascular targeted photodynamic therapy in current clinical practice

Scope: Evaluation of a PSUSA procedure

**Background**

Galcanezumab is a humanised immunoglobulin G4 (IgG4) monoclonal antibody that binds calcitonin gene-related peptide (CGRP). It is indicated, as Emgality, for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Emgality (galcanezumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on serious hypersensitivity reactions. Therefore, the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a detailed causality analysis of cases of serious delayed hypersensitivity reactions.

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

### 6.1.2. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202009

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

**Background**

Niraparib is an inhibitor of poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP) enzymes indicated, as Zejula, in monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO[29] stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy and for maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

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

[28] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[29] International Federation of Gynecology and Obstetrics

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zejula (niraparib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add cognitive impairment as an undesirable effect with a frequency 'common' and to mention it as influencing the ability to drive. Therefore, the current terms of the marketing authorisation(s) should be varied[30].

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

### 6.1.3. Sirolimus - RAPAMUNE (CAP) - PSUSA/00002710/202009

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

**Background**

Sirolimus is a macrolide immunosuppressant indicated, as Rapamune, for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is also indicated for the treatment of patients with sporadic lymphangioleiomyomatosis (LAM) with moderate lung disease or declining lung function.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Rapamune (sirolimus) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the drug-drug interaction between sirolimus and letermovir as a CYP3A4[31] inhibitor. Therefore, the current terms of the marketing authorisation(s) should be varied[32].
- In the next PSUR, the MAH should provide an updated cumulative review of cases on sirolimus exposure during pregnancy, including pregnancies fathered by men exposed to sirolimus, or during lactation/breast feeding and discuss whether an update of the product information is warranted. In addition, the MAH should provide a discussion on off-label use.

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

[30] Update of SmPC sections 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion
[31] Cytochrome P450 3A4
[32] Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

### 6.1.4. Teriflunomide - AUBAGIO (CAP) - PSUSA/00010135/202009

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**Background**

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

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Aubagio (teriflunomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add pulmonary hypertension to the existing warning on respiratory reactions and as an undesirable effect with a frequency 'not known'. In addition, colitis should be added as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied[33].
- In the next PSUR, the MAH should provide a cumulative review of cases of painful musculoskeletal syndrome, including a causality assessment and a discussion on the plausible biological mechanism. The MAH should also provide cumulative reviews of cases of acute kidney injury and of serious dental and gingival conditions. In light of these reviews, the MAH should discuss 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.

### 6.1.5. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/202009

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

**Background**

Vortioxetine is a serotonin reuptake inhibitor indicated, as Brintellix, for the treatment of major depressive episodes in adults.

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

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Brintellix (vortioxetine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add headache and hyperprolactinaemia as undesirable effects with a frequency 'not known' as well as to add hyperhidrosis with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAH should provide a cumulative review of cases of movement disorders from clinical trials, literature and post-marketing data and include a discussion on the need to update the product information as warranted.

The frequency of PSUR submission should be revised from yearly to 2-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

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

See also Annex I 16.2.

### 6.2.1. Leflunomide - ARAVA (CAP); LEFLUNOMIDE MEDAC (CAP); LEFLUNOMIDE ZENTIVA (CAP); NAP - PSUSA/00001837/202009

Applicants: Medac Gesellschaft fur klinische Spezialpraparate mbH (Leflunomide medac), Sanofi-Aventis Deutschland GmbH (Arava), Zentiva, k.s. (Leflunomide Zentiva), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

**Background**

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) agent with antiproliferative properties indicated for the treatment of adult patients with active rheumatoid arthritis and active psoriatic arthritis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Arava, Leflunomide Medac and Leflunomide Zentiva, centrally authorised medicines containing leflunomide, and nationally authorised medicine(s) containing leflunomide 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 leflunomide-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.

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

- The MAH for the originator leflunomide-containing product should submit to EMA, within 60 days, a cumulative review of cases of serious infections, including opportunistic infections and varicella-zoster infections that occurred in patients receiving leflunomide in combination with other immunosuppressant medicinal products. The MAH should also include a discussion on patient characteristics that may influence the risk of severe infections in patients using leflunomide monotherapy versus patients using combination therapy. The cumulative review should be limited to information from clinical trials and published literature studies. A discussion on the need to update the product information should be included as warranted.
- The MAHs for the originator leflunomide-containing product and centrally authorised leflunomide containing products should submit to EMA, within 60 days, a cumulative review of skin ulcer, including a review of data from clinical trials and literature and discuss whether there is a 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.

PRAC considered that the MAH(s) for nationally approved product(s) containing leflunomide, part of the current procedure, should review cases of skin ulcer and discuss the need for an update of the product information as warranted. Further consideration is to be given at CMDh.

### 6.2.2. Thalidomide - THALIDOMIDE CELGENE (CAP); NAP - PSUSA/00002919/202010

Applicants: Celgene Europe BV (Thalidomide Celgene), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

**Background**

Thalidomide is a tumour necrosis factor-alfa (TNF-α) protein synthesis inhibitor indicated, in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Thalidomide Celgene, a centrally authorised medicine containing thalidomide, and nationally authorised medicine(s) containing thalidomide 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 thalidomide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on thyroid disorders and monitoring of the thyroid function. Therefore, the current terms of the marketing authorisations should be varied[35].

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

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

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

See also Annex I 16.3.

### 6.3.1. Terizidone (NAP) - PSUSA/00002904/202009

Applicant(s): various

PRAC Lead: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

**Background**

Terizidone is a pyrazinamide indicated in antituberculosis combination therapy in adults for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing terizidone 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 terizidone-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

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.

PRAC considered that the MAH Riemser Pharma GmbH should further review cases reporting myelosuppressive effect of terizidone or its metabolite cycloserine and discuss the need for an update of the product information as warranted. Further consideration is to be given at CMDh.

### 6.3.2. Tobramycin[36] (NAP) - PSUSA/00009318/202009

Applicant(s): various

PRAC Lead: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

**Background**

Tobramycin is an antibiotic of the aminoglycoside group that is active in vivo and in vitro against a wide variety of gram-negative aerobic bacillus as well as against some gram-negative bacillus-cocci and gram-positive cocci. It is indicated for systemic use for the

[36] Systemic use only

treatment of infections produced by tobramycin-sensitive germs: central nervous system (CNS) infections including meningitis, septicaemia and neonatal sepsis; gastrointestinal infections such as peritonitis; recurrent complicated urinary tract infections including pyelonephritis and cystitis, lower respiratory tract infections including pneumonia, bronchopneumonia and acute bronchitis; infections of bones, soft tissues and skin as well as burns.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing tobramycin for systemic use 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 tobramycin[37]-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the increased risk of ototoxicity in patients with mitochondrial deoxyribonucleic acid (DNA) mutations. Therefore, the current terms of the marketing authorisation(s) should be varied[38].
- In the next PSUR, MAHs should provide cumulative reviews of cases of Bartter-like syndrome and pseudomembranous colitis/Clostridium difficile infection based on literature and post-marketing data and discuss whether an update of the product information is warranted. In addition, MAHs should further explore the penetrance of the mitochondrial DNA mutation in ototoxicity. Finally, MAHs should closely monitor cases of tobramycin resistance in Pseudomonas aeruginosa infections, as well as cases reporting misuse with different routes of administration of tobramycin-containing products.

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. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/LEG 016.2

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 016.1 [analysis of available mortality data from controlled clinical trials in the dexmedetomidine development programme as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00000998/201903) adopted in November 2019] as per the request for supplementary information (RSI) adopted in October 2020

**Background**

[37] For systemic use
[38] Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Dexmedetomidine is a selective alfa-2 receptor agonist indicated, as Dexdor, a centrally authorised product, for sedation of adult intensive care unit (ICU) patients requiring a sedation level not deeper than arousal in response to verbal stimulation and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

Following the evaluation of the most recently submitted PSUR for the above-mentioned medicine(s), PRAC requested the MAH to submit further mortality data from controlled clinical trials in the dexmedetomidine development programme. For background, see PRAC minutes November 2019[39] and PRAC minutes October 2020[40]. The responses to the request for supplementary information (RSI) adopted in October 2020 were assessed by the Rapporteur for further PRAC advice.

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

- The MAH should submit to EMA, within 30 days, a review of the recently published study by *Hughes et al*[41]*.* These data should also be discussed in the context of the consistency of mortality estimates in the younger age group in the trials from the development programme and the study by *Shehabi et al*[42]*.* In addition, the MAH should discuss a proposal to update the product information and the RMP. Finally, the MAH should discuss the need for a direct healthcare professional communication (DHPC) together with a communication plan.

### 6.4.2. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 159.1

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 0159 [review on administration of live vaccines, including a literature review on postnatal clearance of tumour necrosis factor alfa (TNFα) inhibitors in the newborn, particularly of infliximab and of cases of disseminated BCG 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] as per the request for supplementary information (RSI) adopted in December 2020

**Background**

Infliximab is tumour necrosis factor alfa (TNF-α) inhibitor indicated, as Remicade, a centrally authorised product, 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 for the above-mentioned medicine(s), PRAC requested the MAH to provide a review on administration of live vaccines to infants after in utero infliximab exposure. For background, see PRAC minutes April 2020 and PRAC minutes December 2020[43]. The responses to the request for supplementary

[39] Held 28-31 October 2019
[40] Held 28 September - 01 October 2020
[41] Dexmedetomidine or propofol for sedation in mechanically ventilated adults with sepsis. New England Journal of Medicine, 2021. 384(15): p. 1424-14369
[42] Shehabi et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019; 380:2506-2517
[43] Held 23-26 November 2020

information (RSI) adopted in December 2020 were assessed by the Rapporteur for further PRAC advice.

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

- The MAH should submit to EMA, within 60 days, a variation to amend[44] the product information with recommendation regarding use of live vaccines in infants after in utero exposure.

### 6.4.3. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/LEG 161.1

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 0161 [cumulative review of cases of abnormal lipid values in clinical studies and literature data on lipid derangements following tumour necrosis factor alfa (TNFα) 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] as per the request for supplementary information (RSI) adopted in December 2020

**Background**

Infliximab is tumour necrosis factor alfa (TNF-α) inhibitor indicated, as Remicade, a centrally authorised product, 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 for the above-mentioned medicine(s), 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 TNFα inhibitor treatment. For background, see PRAC minutes April 2020 and PRAC minutes December 2020[45]. The responses to the request for supplementary information (RSI) adopted in December 2020 were assessed by the Rapporteur for further PRAC advice.

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

- Having considered the available data, the Rapporteur's assessment and considering dyslipidaemia as a class effect of TNF inhibitors, PRAC further confirmed there is sufficient evidence to support a causal association between infliximab and dyslipidaemia.
- The MAH should submit to EMA, within 60 days, a variation to amend[46] the product information to include dyslipidaemia as an undesirable effect with a frequency 'uncommon'.

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

None

[44] Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is to be updated accordingly
[45] Held 23-26 November 2020
[46] Update of SmPC section 4.8. The package leaflet is to be updated accordingly

## 6.6. Expedited summary safety reviews[47]

### 6.6.1. Coronavirus (COVID-19) mRNA[48] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 002.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Fourth expedited monthly summary safety report for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-19) pandemic

**Background**

Nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as Comirnaty, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people aged 16 years and older.

PRAC assessed the fourth monthly summary safety report (MSSR) for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

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

- PRAC further requested the MAH for Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) to submit to EMA a variation to include extensive limb swelling as an undesirable effect. The MAH should propose a frequency category accordingly.
- In the next MSSR, the MAH should provide reviews and data including refined observed/expected (O/E) analyses and a review of cases suggestive of thrombosis in combination with thrombocytopenia. In addition, the MAH should include a cumulative review of myocarditis and pericarditis from all available sources. The MAH should discuss any plausible mechanisms and whether any risk factors could be identified. A proposal to update the product information including relevant risk minimisation measures should be included as warranted. The MAH should also present a more in-depth observed/expected (O/E) analyses of adverse event of special interest (AESI) for myocarditis and pericarditis. Finally, the MAH should include a review on exposure to Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) during pregnancy.
- In the next PSUR, the MAH should discuss cases of hypoglycemia not limited to patients with type 1 diabetes mellitus (T1DM), a cumulative review focused on serious hypertension and a review of cases suggestive of haemophagocytic syndrome.

### 6.6.2. Coronavirus (COVID-19) mRNA[49] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 011.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: Third expedited monthly summary safety report for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) during the coronavirus disease (COVID-

[47] 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
[48] Messenger ribonucleic acid
[49] Messenger ribonucleic acid

19) pandemic

**Background**

COVID-19 nucleoside-modified messenger ribonucleic acid (mRNA) vaccine is indicated, as COVID-19 Vaccine Moderna, for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults.

PRAC assessed the third monthly summary safety report (MSSR) for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

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

- The MAH for COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) should submit to EMA a variation to add diarrhoea and delayed injection site reactions as undesirable effects. The MAH should propose frequency categories accordingly.
- In the next MSSR, the MAH should provide reviews and data including refined observed/expected (O/E) analyses, a pattern analysis of cases of asthenic conditions, reporting rates of anaphylaxis after the first and second dose of vaccine and an evaluation on the occurrence of hypoesthesia/paraesthesia together other potential reactogenicity symptoms and other potentially vaccine/vaccination related stress-responses. The MAH should provide an evaluation of appendicitis and any new cases suggestive of thrombosis in combination with thrombocytopenia. In addition, the MAH should include a cumulative review of cases of myocarditis and pericarditis together with a more in-depth observed/expected (O/E) analyses of adverse events of special interest (AESI). Finally, the MAH should include a review on exposure to COVID-19 Vaccine Moderna (COVID-19 mRNA vaccine (nucleoside-modified)) during pregnancy.
- In the next PSUR, the MAH should include a cumulative review of serious cases of hypertension. The MAH should discuss any plausible mechanisms and whether any risk factors could be identified. A discussion on the need to update the product information including relevant risk minimisation measures should be provided as warranted.

### 6.6.3. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First expedited monthly summary safety report for Janssen COVID-19 Vaccine (COVID-19 vaccine (Ad26.COV2-S, recombinant)) during the coronavirus disease (COVID-19) pandemic

**Background**

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated as COVID-19 vaccine Janssen, a centrally authorised vaccine for active

immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the first monthly summary safety report (MSSR) for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant]) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

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

- In the next MSSR, the MAH should provide thorough reviews of cases of olfactory disorders, dizziness and paraesthesia/dysesthesias. The MAH should further evaluate whether diarrhoea and vomiting may be adverse reactions. In addition, the MAH should include observed/expected (O/E) analyses for encephalitis events, arthritis and gout.

### 6.6.4. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 027.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Second expedited monthly summary safety report for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) during the coronavirus disease (COVID-19) pandemic

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

PRAC assessed the second monthly summary safety report (MSSR) for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) as part of the safety monitoring of the vaccine. At the plenary meeting, PRAC adopted its conclusions.

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

- In the next MSSR, the MAH should provide cumulative reviews of cases of eye pain, photophobia and vision blurred as well as of cases of palpitations and tachycardia. The MAH should also include a cumulative review of cases of Guillain-Barre syndrome (GBS) including a classification of cases according to the case definition of the Brighton Collaboration and a causality assessment.
- In the next PSUR, the MAH provide cumulative reviews of serious hypertension, mucocutaneous bleeding and herpes infection.

### 6.6.5. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/LEG 036.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to LEG 036 [cumulative review of cases of hypersensitivity as per the conclusions of the signal procedure (EPITT 19668) adopted in March 2021] as per the

request for supplementary information adopted in April 2021

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

PRAC assessed a thorough analysis of cases of hypersensitivity including anaphylaxis as requested in the recommendation adopted in March 2021 in the context of the signal of anaphylactic reactions (EPITT 19668). PRAC further assessed the responses from the MAH to the request for supplementary information adopted in April 2021. At the organisational, regulatory and methodological matters (ORGAM)[50] meeting held on 20 May 2021, PRAC discussed adopted its conclusions. For further background, see PRAC minutes March 2021 and PRAC minutes April 2021.

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

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should submit to EMA, within 15 days, a variation to include urticaria and angioedema as undesirable effects with a frequency uncommon and not known respectively. This will be assessed as part of ongoing variation II/002.

### 6.6.6. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.7

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Ninth expedited summary safety report (SSR) for Veklury (remdesivir) during the coronavirus disease (COVID-19) pandemic

**Background**

Remdesivir is an adenosine nucleotide prodrug indicated, as Veklury, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen, under certain conditions.

PRAC assessed the ninth summary safety report (SSR) for Veklury (remdesivir) as part of the safety monitoring of the medicinal product. At the organisational, regulatory and methodological matters (ORGAM)[51] meeting on 20 May 2021, PRAC adopted its conclusions.

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

- PRAC agreed on the need to update the existing warning of the product information to on anaphylactic reaction to monitor patients for hypersensitivity reactions during and following administration of remdesivir. In addition, anaphylactic reaction should be added as an undesirable effect with a frequency 'not known'. See under 8.2.1.

[50] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)
[51] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

- In the next PSUR[52], the MAH should provide a review of cases of acute pancreatitis.
- In light of the safety profile of remdesivir and submission of PSURs, PRAC agreed that submission of further SSR is not warranted any longer.

# 7. Post-authorisation safety studies (PASS)

## 7.1. Protocols of PASS imposed in the marketing authorisation(s)[53]

See also Annex I 17.1.

### 7.1.1. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/PSP/S/0093

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Protocol for an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risks of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring contribute to assess the effectiveness of risk minimisation measures

**Background**

Fenfluramine is a serotonin releasing agent indicated, as Fintepla, for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

In order to fulfil the specific obligation to conduct a PASS (Annex II-D) imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH Zogenix ROI Limited submitted to EMA a protocol version 1.0 for a study entitled: 'a registry of subjects with Dravet syndrome treated with fenfluramine' for review by PRAC in order to assess long-term cardiac safety of fenfluramine prescribed in routine practice. PRAC is responsible for evaluating the PASS protocol.

**Endorsement/Refusal of the protocol**

- PRAC, having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above-listed medicinal product(s). PRAC agreed that the PASS is non-interventional, but the study design does not fulfil the study objectives at this stage.
- The MAH should include valvulopathy as a primary endpoint besides valvular heart disease (VHD). The primary outcome variables should be also revised. Regarding severity criteria, PRAC supported using the European Society of Cardiology as a reference. The MAH should also include appropriate reference to the respective guideline or literature for each listed condition. For pulmonary arterial hypertension (PAH), the source document for case definition for the registry should be provided. In relation to database research methods, the MAH should discuss whether it is feasible to include an

[52] Data lock point (DLP): 06 May 2021
[53] In accordance with Article 107n of Directive 2001/83/EC

Italian data source, given the presence of several treatment centres in the collaborating Dravet treatment networks in this Member State. The MAH should also consider age distribution of study participants at cohort entry when conducting the database study and ensure the same study endpoints are observed for both the registry and database study. Moreover, 'physicians' adherence to the echocardiogram monitoring plan' as a secondary objective. Finally, PRAC agreed that the MAH should ensure that selected databases capture information about the performance of electrocardiograms (ECG), and that diagnostic suspicion bias is considered when interpreting the results.

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

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[54]

See also Annex I 17.2.

### 7.2.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant]) - COVID-19 VACCINE JANSSEN (CAP) - EMEA/H/C/005737/MEA 007

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study VAC31518COV4005 (listed as a category 3 study in the RMP): COVID-19 vaccines International Pregnancy Exposure Registry (C-VIPER) to assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with COVID-19 vaccine (Ad26.COV2-S, recombinant) during pregnancy [final study report expected in June 2027]

**Background**

Coronavirus (COVID-19) vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein. It is indicated, as COVID-19 vaccine Janssen, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

As stated in the RMP of COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant])), the MAH is requested to conduct a study entitled 'COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)' to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID-19 vaccine. The protocol submitted is generic for all COVID-19 vaccines. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. At the organisational, regulatory and methodological matters (ORGAM)[55] meeting on 20 May 2021, PRAC adopted its conclusions.

**Summary of advice**

- Based on the review of protocol version 1.2 and the assessment from the Rapporteur, PRAC considered the protocol for COVID-19 vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant]) is acceptable. The C-VIPER protocol is in all essential

[54] 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
[55] Extended to specific COVID-19-related procedure(s) during EMA business continuity plan (BCP)

aspects in line with previous outcome of PRAC assessment of the protocol for other COVID-19 vaccines.

### 7.2.2. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 007

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for study D8111R00006: a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to COVID-19 vaccine (ChAdOx1-S [recombinant] (AZD1222/Vaxzevria) and safety concerns (from initial opinion/marketing authorisation)

**Background**

Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is indicated, as Vaxzevria, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

As stated in the RMP of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])), the MAH is requested to conduct a post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to its COVID-19 vaccine and safety concerns. The MAH submitted a protocol for study D8111R00006 to evaluate the incidence and relative risk of safety concerns and adverse events of special interest (AESI) following immunisation with Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) in the real-world setting. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

**Summary of advice**

- Based on the review of protocol version 1.0 and the assessment from the Rapporteur, PRAC considered the protocol for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) could be acceptable provided that an updated protocol is submitted to EMA. The MAH should provide further data and clarifications.
- In particular, the MAH should add 'thrombosis associated with thrombocytopenia (TTS)' to the list of AESI under investigation. The MAH should also include further details on data extraction, definition of covariates and measurement of propensity score in the statistical analysis plan (SAP). In addition, the MAH should further discuss the feasibility of the study and consider including additional EU databases to complement those proposed. The MAH should also discuss the availability of information on pregnancy, pregnancy outcomes and mother-baby linkage in the chosen databases. Moreover, the MAH should include comparative analyses in every interim study report and in line with the published ACCESS[56] protocol template for 'safety evaluation of COVID-19 vaccines in electronic healthcare databases'. Finally, the MAH should revise the milestones dates regarding submissions of progress reports.

[56] vACCine covid-19 monitoring readinESS

## 7.3. Results of PASS imposed in the marketing authorisation(s)[57]

### 7.3.1. Hydroxyethyl starch (HES) (NAP) - EMEA/H/N/PSR/J/0031

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

PRAC Rapporteur: Adrien Inoubli

Scope: Results for a joint 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)

**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.

In line with 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 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 EMA the results of the required drug utilisation study (DUS) entitled 'a retrospective, multinational, 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 further background, see PRAC minutes January 2019, PRAC minutes June 2019, PRAC minutes September 2020[58] and PRAC minutes December 2020[59].

PRAC discussed the final study report for the DUS. PRAC is responsible for evaluating the PASS final results.

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

- Based on the review of the final report of the DUS, PRAC considered that a request for supplementary information (RSI) is necessary before a final recommendation can be made based on the PASS final report.
- In particular, the MAHs should provide clarifications on research methods regarding results of the feasibility and site selections for the study, including details on accredited sites and data for the nine EU-countries part of the study. The MAHs should further comment on limitations relating to site exclusions. Further details on patient demographics are needed and on non-adherent prescriptions. Moreover, a thorough discussion on the key results should be added, including an ad-hoc analysis comparing

[57] In accordance with Article 107p-q of Directive 2001/83/EC
[58] Held 31 August - 03 September 2020
[59] Held 23-26 November 2020

the results of previous DUSs to the present DUS for the same sites, information on contraindicated use in critically ill patients including those with sepsis. Finally, the MAHs should include a thorough discussion regarding the non-compliance with implemented risk minimisation measures to identify factors that can improve product information adherence at sites with low adherence.

- The MAH should submit responses to the RSI within 60 days to EMA. 60 day-assessment timetable will be followed.

### 7.4. Results of PASS non-imposed in the marketing authorisation(s)[60]

See Annex I 17.4.

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

See Annex I 17.5.

### 7.6. Others

See Annex I 17.6.

### 7.7. New Scientific Advice

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

### 7.8. Ongoing Scientific Advice

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

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

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

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

### 8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

### 8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

[60] 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

### 8.2.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/R/0015 (with RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

**Background**

Remdesivir is an adenosine nucleotide prodrug indicated, as Veklury, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen, under certain conditions.

Veklury, a centrally authorised product containing remdesivir, was authorised under a conditional marketing authorisation in 2020. Based on the fulfilment of specific obligation(s) and safety data, the MAH submitted a request for yearly renewal of the marketing authorisation for opinion by CHMP. PRAC is responsible for providing advice to CHMP on this conditional renewal with regard to safety and risk management aspects. For further background, see PRAC minutes March 2021.

**Summary of advice**

- Based on the review of the status of the fulfilment of specific obligations (SO), safety data submitted for Veklury (remdisivir), the joint CHMP-PRAC Rapporteurs' assessment report including the evaluation of the MAH's responses to the request for supplementary information (RSI), PRAC considered that the conditional renewal could be finalised if satisfactory clarification is given on some pending issues. Regarding the RMP, it could be considered acceptable provided that an update to RMP version 1.3 is submitted. The MAH should include study GS-US-540-5912[61] to the pharmacovigilance plan.
- The update of the product information to add details on anaphylactic reaction to the existing warning on 'hypersensitivity including infusion-related and anaphylactic reactions and to add it as an undesirable effect is implemented within the current procedure. See also 6.6.6.

## 8.3. Renewals of the marketing authorisation

See Annex I 18.3.

# 9. Product related pharmacovigilance inspections

## 9.1. List of planned pharmacovigilance inspections

None

[61] A phase 3 randomized, double-blind, placebo-controlled, parallel group, multicentre study evaluating the efficacy and safety of remdesivir in participants with severely reduced kidney function who are hospitalised for coronavirus 19 (COVID-19)

## 9.2. Ongoing or concluded pharmacovigilance inspections

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

## 9.3. Others

None

# 10. Other safety issues for discussion requested by 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

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

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

## 11.1. Safety related variations of the marketing authorisation

None

## 11.2. Other requests

None

# 12. Organisational, regulatory and methodological matters

## 12.1. Mandate and organisation of PRAC

### 12.1.1. PRAC efficiency and workload – optimisation in the context of the business continuity plan due to coronavirus 19 (COVID-19)

PRAC Lead: Sabine Straus, Martin Huber

The EMA Secretariat presented short-term measures in order to optimise PRAC efficiency and workload in the context of the business continuity plan due to COVID-19-related procedures. PRAC agreed with the measures.

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

None

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

### 12.3.1. Scientific Advisory Groups (SAG) – mandate renewals and nominations for therapeutic SAGs

The EMA Secretariat presented to PRAC a call for nomination for the Inter-committee Scientific Advisory Group On Oncology (SAG-O). PRAC members were invited to propose experts for appointment as core members by 04 June 2021. PRAC was also informed that a public call for expression of interests for renewal of mandate for all therapeutic SAGs was launched early May 2021. The call runs for two months and is published on the EMA website (EMA/170106/2019).

## 12.4. Cooperation within the EU regulatory network

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

The EMA Secretariat updated 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.

### 12.4.1. European Centre for Disease Prevention and Control (ECDC) recommendations on adverse reactions to COVID-19 vaccination and the safety of substances of human origin

At the organisational, regulatory and methodological matters (ORGAM) meeting on 20 May 2021, the EMA Secretariat presented for comments to PRAC the draft European Centre for Disease Prevention and Control (ECDC) recommendations on adverse reactions to COVID-19 vaccination and the safety of substances of human origin (SoHO) and further discussion at the COVID-19 EMA pandemic Task Force (ETF) and CHMP.

Post-meeting note: On 03 June 2021, ECDC published their recommendation on their website.

### 12.4.2. Joint advisory board (JAB) for COVID-19 vaccines studies – feedback and update on COVID-19 observational vaccine safety studies

As a follow-up to the discussion held in April 2021 (for background, see PRAC minutes April 2021), the EMA Secretariat further updated PRAC on progress of the EMA safety monitoring plan, including the early safety study, the extension of the ongoing coagulopathy study with a vaccinated cohort, the 2-year large safety study to start mid-2021, and an upcoming EMA-funded etiological study to measure the association between COVID-19 vaccines and

thrombosis with thrombocytopenia syndrome (TTS)/thromboembolic events. PRAC members were invited to send comments by 10 May 2021 on the tender specifications for the EMA study. Finally, PRAC was also updated on vaccine effectiveness activities led by the European Centre for Disease Prevention and Control (ECDC) and on the recent ECDC/EMA Joint Advisory Board (JAB) on COVID-19 vaccine monitoring held on 26 April 2021.

## 12.5. Cooperation with International Regulators

None

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

None

## 12.7. PRAC work plan

None

## 12.8. Planning and reporting

### 12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators - Q1 2021 and predictions

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see PRAC minutes February 2021.

### 12.8.2. Marketing authorisation applications (MAA) – 3-year forecast (March 2021 – December 2023)

The EMA Secretariat presented to PRAC for information a 3-year forecast covering the period March 2021-December 2023 on marketing authorisation applications (MAA) planned for submission (the business 'pipeline'). Quarterly reports will be prepared to keep Committees informed of the evolution of current year forecast of initial MAA.

## 12.9. Pharmacovigilance audits and inspections

### 12.9.1. Pharmacovigilance systems and their quality systems

None

### 12.9.2. Pharmacovigilance inspections

None

### 12.9.3. Pharmacovigilance audits

None

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

### 12.10.1. Periodic safety update reports

None

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

PRAC Lead: Menno van der Elst, Maia Uusküla

PRAC was updated on the activities of the Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list and noted the GPAG progress highlights.

### 12.10.3. PSURs repository

None

### 12.10.4. Union reference date list - consultation on the draft list

PRAC endorsed the draft revised EURD list, version May 2021, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of May 2021, the updated EURD list was adopted by CHMP and CMDh at their May 2021 meetings and published on the EMA website on 26 May 2021, see:

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

## 12.11. Signal management

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

PRAC Lead: Menno van der Elst

The EMA Secretariat provided PRAC with a brief update from the Signal Management Review Technical (SMART) working group work stream on 'Methods' to inform the Committee that a dashboard was created in EudraVigilance data analysis system (EVDAS) to show aggregated EudraVigilance (EV) data on all centrally authorised COVID-19 vaccines. Further update will be given in June/July 2021.

## 12.12. Adverse drug reactions reporting and additional reporting

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

None

### 12.12.2. Additional monitoring

None

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

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 26 May 2021, see:

Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

## 12.13. EudraVigilance database

### 12.13.1. Activities related to the confirmation of full functionality

None

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

### 12.14.1. Risk management systems

None

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

None

### 12.14.3. Coronavirus (COVID-19) pandemic - coreRMP19: variants guidance for RMP requirements, traceability and others – restart of drafting group

At the organisational, regulatory and methodological matters (ORGAM) meeting on 20 May 2021, the EMA Secretariat informed PRAC of the restart of the drafting group to revise the 'Consideration on core requirements for RMPs of COVID-19 vaccines' document published in November 2020 in order to reflect the experience with RMP and monthly summary safety reviews (MSSR) assessment for COVID-19 vaccines, requirements for variants and new strains variations. Further discussion is planned in June 2021.

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

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

None

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

None

## 12.16. Community procedures

### 12.16.1. Referral procedures for safety reasons

None

## 12.17. Renewals, conditional renewals, annual reassessments

None

## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

None

### 12.18.2. Safety communication

None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

None

## 12.20. Others

### 12.20.1. Drug-induced hepatotoxicity - PRAC assessors' guide - update

PRAC Lead: Menno van der Elst, Martin Huber

Following the adoption of the PRAC assessors' guide on drug-induced hepatotoxicity/drug-induced liver injury (DILI) in July 2020 (for background, see PRAC minutes July 2020), the EMA Secretariat presented to PRAC an updated guide taking into account assessors' and member's feedback gained so far. PRAC adopted the revised guide.

### 12.20.2. Procedural guidance for variant strain(s) update for coronavirus-19 (COVID-19) vaccines - draft

At the organisational, regulatory and methodological matters (ORGAM) meeting on 20 May 2021, the EMA Secretariat presented to PRAC a draft procedural guidance for variant strain(s) updates to for coronavirus-19 (COVID-19) vaccines highlighting key aspects for traceability. PRAC members were invited to send comments by 24 May 2021.

Post-meeting note: the 'Procedural guidance for variant strain(s) update to vaccines intended for protection against Human coronavirus' was adopted by CHMP on 24 June 2021 (EMA/175959/2021) and published on the EMA website.

### 12.20.3. Rapid data analytical process - Final report

PRAC Lead: Sabine Straus

Following the presentation in 2020 of the interim report on the pilot initiative on rapid data analytics (for background, see PRAC minutes July 2020) and in line with the PRAC work plan 2021, the EMA Secretariat presented to PRAC the draft final report on the rapid data analytical process. The pilot should be seen in the context of the use of real-world evidence (RWE) in the development, authorisation and supervision of medicines to facilitate decision-making. The pilot for rapid data analyses was performed by EMA from November 2019 to January 2021 to test the feasibility and usefulness of a process for rapid identification, analysis and reporting of results of epidemiological questions arising in the context of regulatory assessments by PRAC. As next steps, PRAC members are invited to respond to an EMA survey on the draft final report by 24 May 2021 in view to publish the executive summary of the final report.

Post-meeting note: On 27 July 2021, the report on PRAC pilot on rapid data analytics (EMA/421578/2021) was published on the EU PAS Register/ENCePP website (https://www.encepp.eu/encepp/viewResource.htm?id=42291).

### 12.20.4. Video conferencing tool - WebEx rollout plan for PRAC

The EMA Secretariat presented to PRAC the Webex rollout plan for PRAC. The first Webex virtual PRAC meeting will take place in June 2021. Trainings and practice run sessions will be organised by PRAC Secretariat in advance of the next plenary meeting.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation[62]

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

As per agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[63].

### 14.1.1. Ipilimumab – YERVOY (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of transverse myelitis

[62] 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

[63] Either MAH(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

EPITT 19677 – New signal

Lead Member State(s): NL

#### 14.1.2. Ponatinib – ICLUSIG (CAP)

Applicant(s): Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Signal of panniculitis

EPITT 19681 – New signal

Lead Member State(s): SE

### 14.2. New signals detected from other sources

## 15. Annex I – Risk management plans

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

As per agreed criteria, 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. Icatibant - EMEA/H/C/005083

Scope: Treatment of hereditary angioedema

#### 15.1.2. Ranibizumab - EMEA/H/C/005545

Scope: Treatment of neovascular age-related macular degeneration (AMD)

#### 15.1.3. Sitagliptin - EMEA/H/C/005598

Scope: Treatment of type 2 diabetes mellitus (T2DM)

#### 15.1.4. Sugammadex - EMEA/H/C/005403

Scope: Treatment of neuromuscular blockade induced by rocuronium or vecuronium

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

As per agreed criteria, 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. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0033

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Submission of an updated RMP (version 3.1) in order to remove the safety concern of 'long term safety' as missing information based on a report of the cumulative safety data from pivotal study BO28984 (ALEX): a randomized, multicentre, phase 3, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer (NSCLC). In addition, the MAH took the opportunity to update the RMP to remove from the pharmacovigilance plan study BO40643: a survey measuring the effectiveness of the risk minimisation activities to prescribers: correct implementation of Alecensa (alectinib) label guidance by prescribers of the following important identified risks: interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, photosensitivity, bradycardia, severe myalgia and creatine phosphokinase (CPK) elevations, following the conclusions of variation II/0030 concluded in February 2021

### 15.2.2. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/II/0054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 4.4) to include several updated study milestones and to bring it in line with revision 2 of GVP module V on 'Risk management systems'

### 15.2.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/II/0092

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 40) in order to add study 213928 (as a category 3 study in the RMP): a prospective cohort study based on the existing infrastructure of Teratology Information Services (TIS) within the Unites States (US) and Canada to evaluate pregnancy and infant outcomes for pregnancies in women with systemic lupus erythematosus (SLE) exposed to belimumab, as an alternative pregnancy exposure study for the missing information on limited data in pregnant and lactating patients. The RMP includes also the completion date and effectiveness for the distribution of the direct healthcare professional communication (DHPC) in relation to the important identified risk of psychiatric events including depression and suicidality

### 15.2.4. Bevacizumab - AYBINTIO (CAP) - EMEA/H/C/005106/WS2040/0004/G; ONBEVZI (CAP) - EMEA/H/C/005640/WS2040/0001/G

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) submission of updated RMP (version 4.0 for Aybintio, version 2.0 for Onbevzi) to remove the missing information of 'long term effects of bevacizumab when used in the paediatric population' in order to align the safety concerns to those of the medicinal product of reference; 2) update of sections 4.4, 5.1 and 6.6 of the SmPC following assessment of the same changes for the medicinal product of reference (variation IB/0118 finalised in January 2021). In addition, the MAH took the opportunity to introduce minor changes in the SmPC and to align the product information for Onbevzi

(bevacizumab) with the latest quality review of documents (QRD) template (version 10.2)

### 15.2.5. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0015

Applicant: Merck Europe B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of an updated RMP (version 1.5) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to include long-term safety data from the completed PREMIERE registry: a prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical studies; and to remove it from the pharmacovigilance plan. Furthermore, the status of the post-approval safety study MS 700568-0002: a long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine (CLARION); and study MS 700568-0004: pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study (CLEAR). Finally, the RMP is updated in line with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010634/201907) adopted in January 2020

### 15.2.6. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS2013/0092; BINOCRIT (CAP) - EMEA/H/C/000725/WS2013/0091; EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS2013/0091

Applicant: Sandoz GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of an updated RMP (version 18) for Abseamed, Binocrit, Epoetin Alfa Hexal in line with the RMP of the medicinal product of reference consisting of: 1) replacement of the term 'tumour growth potential' with 'disease progression' and 'premature death' with 'survival impact'; 2) clinical study data on these two topics were shortened; 3) removal of TRIGONS study proposal (MEA18; HX575-502) as additional pharmacovigilance activity. The risks of disease progression and survival impact will be monitored by routine pharmacovigilance and continue to be reviewed in PSURs

### 15.2.7. Lopinavir, ritonavir - LOPINAVIR/RITONAVIR MYLAN (CAP) - EMEA/H/C/004025/II/0016

Applicant: Mylan S.A.S

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 4.0) in order to bring the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and revision 2 of GVP module V on 'Risk management systems' and to align the safety concerns with those of the reference medicinal product

### 15.2.8. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/II/0026, Orphan

Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 1.2) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template) and to add clinical studies (listed as specific obligations in Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation') to the pharmacovigilance plan, namely study 747-302: a phase 4, double-blind, randomized, placebo-controlled, multicentre study evaluating the effect of obeticholic acid on clinical outcomes in patients with primary biliary cholangitis; and study 747-401: a phase 4, double-blind, randomized, placebo-controlled study evaluating the pharmacokinetics and safety of obeticholic acid in patients with primary biliary cholangitis and moderate to severe hepatic impairment; as agreed in the conclusions of the conditional renewal procedure (R/0023) finalised in November 2020. Other changes also include an update to the exposure data from clinical studies, addition of data on post-marketing experience and addition of some specific relevant SmPC wording in the risk minimisation measures

### 15.2.9. Rotavirus vaccine (live, oral) - ROTATEQ (CAP) - EMEA/H/C/000669/II/0085

Applicant: MSD Vaccins

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 7.2) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems'. As a consequence, the list of safety concerns is updated and a reclassification of important risks is proposed. In addition, the updated RMP includes the removal of hypersensitivity and severe combined immunodeficiency (SCID) from the list of safety concerns as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002666/201911) adopted in June 2020

### 15.2.10. Sildenafil - REVATIO (CAP) - EMEA/H/C/000638/II/0091

Applicant: Upjohn EESV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 7.0) in line with revision 2 of GVP module V on 'Risk management systems'. Consequently, the educational programme for the risk of hypotension is proposed to be terminated

### 15.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0038

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP (version 17.1) in order to incorporate study A3921348: a US-based drug utilisation study (DUS) using either electronic health records (HER) or administrative claims database into study A3921347: a prospective non-interventional active surveillance study in the US to quantify the incidence of key safety events of interest in moderate-to-severe UC patients treated with tofacitinib and other systemic therapies in the clinical practice (real world) setting (both listed as category 3 studies in the RMP)

### 15.2.12. Vildagliptin - GALVUS (CAP) - EMEA/H/C/000771/WS1970/0067; JALRA (CAP) - EMEA/H/C/001048/WS1970/0069; XILIARX (CAP) - EMEA/H/C/001051/WS1970/0067; vildagliptin, metformin hydrochloride - EUCREAS (CAP) - EMEA/H/C/000807/WS1970/0081; ICANDRA (CAP) - EMEA/H/C/001050/WS1970/0084; ZOMARIST (CAP) - EMEA/H/C/001049/WS1970/0083

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 15.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and aligned with the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00003113/201802) adopted in October 2018. In addition, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' of the product information is updated to remove the statement on submission of an RMP update every 3 years

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

As per agreed criteria, 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. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/X/0061/G

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (2.5 mg film-coated tablet); 2) extension of indication to include paediatric use (8 to less than 18 years). The RMP (version 9.0) is updated accordingly

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

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 ≥ 12 to < 18 years, weighing ≥ 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. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0038, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the use of blinatumomab as monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor acute lymphoblastic leukaemia (ALL) as consolidation therapy. 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 13.0) are updated in accordance

### 15.3.4. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0021, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.2 of the SmPC in order to modify administration instructions to include the option of self/carer-administration based on results from two interventional clinical safety and efficacy studies, namely: 1) study KRN23-003: a phase 3 open-label trial to assess the efficacy and safety of burosumab (KRN23) in paediatric patients with X-linked hypophosphaetemic rickets/osteomalacia (final study report); 2) study KRN23-004: a phase 3 long-term extension study of burosumab in adult patients with X-linked hypophosphataemic rickets/osteomalacia and a post-marketing study of burosumab switched from the phase 3 long-term extension study (interim report). The package leaflet is updated accordingly and includes a new section with instructions for use. In addition, the MAH took the opportunity to implement editorial changes throughout the product information. The RMP (version 3.0) is also updated in accordance

### 15.3.5. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1941/0043; FORXIGA (CAP) - EMEA/H/C/002322/WS1941/0062

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of chronic kidney disease. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Forxiga and Edistride (dapagliflozin) are updated based on the results from the renal outcomes study D169AC00001 (DAPA-CKD) (listed as a category 3 study in the RMP): a multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study evaluating the effect of dapagliflozin versus placebo given once daily in addition to standard of care to evaluate the potential risk of lower limb amputation to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death. Annex II-B on 'Conditions or restrictions regarding supply and use' and the package leaflet are updated accordingly. The RMP (version 22.1) is also updated in accordance

### 15.3.6. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/II/0018/G, Orphan

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) extension of indication to add treatment of relapsed/refractory Acute myeloid leukaemia (AML) in paediatric patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the

new safety and efficacy data from the paediatric clinical study AAML1421: a phase 1/2 study of liposomal daunorubicin/cytarabine alone followed by fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) (FLAG) for children with relapsed AML. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the product information is updated in line with the latest quality review of documents (QRD) template (version 10.2); 2) submission of the final data from paediatric clinical study CPX-MA-1201: a phase 1/pilot study of liposomal daunorubicin/cytarabine for children, adolescents and young adults with recurrent or refractory hematologic malignancies, in support of the extension of indication

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

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 Deltyba (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. Annex II is updated to remove the specific obligation related to an in vitro study using the hollow fibre system model of tuberculosis (HFS-TB)

### 15.3.8. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0069/G

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC in order to add rhinorrhoea to the list of adverse drug reactions (ADRs) with frequency not known based on a systematic review of information from clinical and non-clinical studies, post-marketing data and scientific literature. The package leaflet has been updated accordingly; 2) update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 109MS303 (ENDORSE) (listed as a category 3 study in the RMP): a dose-blind, multicentre, extension study to determine the long-term safety and efficacy of two doses of BG00012 (dimethyl fumarate) monotherapy in subjects with relapsing-remitting multiple sclerosis. The RMP (version 11.1) is updated accordingly

### 15.3.9. Erenumab - AIMOVIG (CAP) - EMEA/H/C/004447/II/0013/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC to add alopecia, oral sores and rash in line with revised clinical safety data; 2) update of sections 4.8 and 5.1 of the SmPC based on the study report from 5-year open-label study 20120178: a phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel-group study of subjects with episodic migraine; 3) update of section 5.1 of the SmPC to include of the anatomical therapeutic chemical (ATC) classification system code for erenumab. The package leaflet and the RMP (version 3.0) are updated accordingly

## 15.3.10. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0001

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of active ulcerative colitis 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. In addition, the package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to include minor updates to Annex II and to implement minor editorial changes throughout the product information

## 15.3.11. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0110

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include the prevention of head and neck cancers causally related to certain oncogenic human papillomavirus types. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 23.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

## 15.3.12. Lorlatinib - LORVIQUA (CAP) - EMEA/H/C/004646/II/0015

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from study 1006 (CROWN) (listed as a specific obligation (SOB) in the Annex II): a phase 3 randomised open-label study of lorlatinib monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced ALK-positive NSCLC. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the applicant proposes to downgrade the specific obligation to conduct a single arm study in patients who progressed after alectinib or ceritinib to a recommendation and convert the conditional marketing authorisation to a full marketing authorisation (MA)

## 15.3.13. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0032

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC based on the interim data from the primary vaccination phase (stage 1) of study B1971057: a phase 3, randomised, active-controlled, observer-blinded study to assess the immunogenicity, safety and tolerability of Trumenba (meningococcal group B vaccine) when administered as a 2-dose regimen and a

first-in-human study to describe the immunogenicity, safety and tolerability of a bivalent rLP2086 containing pentavalent vaccine (MenABCWY) in healthy subjects ⩾10 to <26 years of age. The RMP (version 5.0) is updated accordingly. The MAH took the opportunity to implement some editorial changes in section 4.4 of the SmPC and in the package leaflet to introduce 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'

### 15.3.14. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0109

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of SmPC sections 4.4, 4.8 and 5.1 based on the 5-year follow up data from study CAMN107A2203: a multicentre, open label, non-controlled phase 2 study to evaluate efficacy and safety of oral nilotinib in paediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib. Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to reflect the fulfilment of the obligation to conduct the post authorisation efficacy study (PAES). The package leaflet and the RMP (version 24.0) are updated accordingly

### 15.3.15. Pyronaridine, artesunate - PYRAMAX (Art 58[64]) - EMEA/H/W/002319/II/0023/G

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of the submission of the final clinical study reports (CSR) of two completed studies: 1) study SP-C-021-15 (listed as a category 3 study in the RMP): a phase 3b/4 cohort event monitoring study conducted in Central Africa to evaluate the safety in patients after the local registration of Pyramax (pyronaridine/artesunate) (CANTAM study); 2) study SP-C-026-18: a randomized open-label exploratory study to determine the efficacy of different treatment regimens of Pyramax (pyronaridine/artesunate) in asymptomatic carriers of Plasmodium falciparum mono-infections. This non-imposed study was conducted in Gambia and Zambia and compared asymptomatic subjects with parasitaemia dosed according to the approved label of 3-day dosing with 2-day and 1-day dosing. As a consequence, sections 4.2, 4.4, 4.6, 4.8 and 5.1 are updated. The package leaflet is updated in accordance. The RMP (version 17) is also updated accordingly and in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

### 15.3.16. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

[64] 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: Extension of indication to include treatment of adults with pneumonia not requiring supplemental oxygen (moderate COVID-19), based on: 1) part A of study GS-US-540-5774: a phase 3, randomized, open-label, multicentre study comparing 2 remdesivir (RDV) regimens (5 days and 10 days) versus standard of care in 584 participants with moderate COVID 19; 2) study CO-US-540-5776 (adaptive COVID-19 treatment trial (ACTT)): a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored phase 3, multicentre, adaptive, randomized, double blind, placebo controlled trial on the safety and efficacy study of investigational therapeutics for the treatment of COVID-19. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 1.2) are updated in accordance

## 15.3.17. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/X/0067

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension application to introduce a new strength of 75 mg solution for injection. The RMP (version 8.0) is updated accordingly

## 15.3.18. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/X/0021

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Extension application to add a new strength of 2 mg solution for injection. The RMP (version 6.0) is updated accordingly

## 15.3.19. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/X/0045/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (200 mg / 50 mg / 50 mg film-coated tablets). The new presentation is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older or weighing at least 30 kg. In addition, the MAH took the opportunity to implement minor editorial updates in module 3.2.P; 2) extension of indication to include paediatric use in patients aged 12 years and older or weighing at least 30 kg to the existing presentation. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.2) are updated in accordance

## 15.3.20. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0035

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy for Xeljanz (tofacitinib) film-coated tablets. 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 17.1) are updated in

accordance

### 15.3.21. Trastuzumab - ZERCEPAC (CAP) - EMEA/H/C/005209/II/0008

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new fill weight for Zercepac (trastuzumab) powder for concentrate for solution for infusion, 420 mg/vial (EU/1/20/1456/003). The strength (concentration after reconstitution) is identical to the previously authorised finished product 150 mg/vial presentation. The RMP (version 1.2) is updated accordingly

### 15.3.22. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/X/0006/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variations consisting of: 1) extension application to introduce a new strength (30 mg prolonged-release tablet); 2) extension of indication to add treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated in accordance. In addition, the MAH took the opportunity to include a minor update in Annex II

### 15.3.23. Velmanase alfa - LAMZEDE (CAP) - EMEA/H/C/003922/II/0018, Orphan

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4, 4,8 and 5.1 of the SmPC based on the final results of study rhLAMAN-08 (listed as an Annex II study in the RMP): a 24-month multicentre, open-label phase 2 trial investigating the safety and efficacy of repeated velmanase alfa (recombinant human alfa-mannosidase) treatment in paediatric patients below 6 years of age with alfa-mannosidosis. The package leaflet and the RMP (version 8.1) are updated accordingly. The RMPv8.1 has also been submitted. In addition, the product information is updated in line with the latest quality review of documents (QRD) template (version 10.2)

### 15.3.24. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/II/0031

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Update sections 4.2 and 4.4 of the SmPC on tumour lysis syndrome (TLS) prophylaxis and management following an update to the company core data sheet (CCDS) as result of a medical safety assessment conducted on TLS post-marketing reports

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

Based on the assessment of the following PSURs, 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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202009

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

### 16.1.2. Aztreonam65 - CAYSTON (CAP) - PSUSA/00000283/202009

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

### 16.1.3. Bexarotene - TARGRETIN (CAP) - PSUSA/00000404/202009

Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

### 16.1.4. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

### 16.1.5. Cariprazine - REAGILA (CAP) - PSUSA/00010623/202010

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

[65] Inhalation use only

Scope: Evaluation of a PSUSA procedure

### 16.1.6. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202009

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### 16.1.7. Chenodeoxycholic acid[66] [67] - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - PSUSA/00010590/202010

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

### 16.1.8. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202009

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### 16.1.9. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202010

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

### 16.1.10. Dibotermin alfa - INDUCTOS (CAP) - PSUSA/00001034/202009

Applicant: Medtronic BioPharma B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### 16.1.11. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202009

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

[66] For the treatment of inborn error in primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults
[67] Centrally authorised product(s) only

### 16.1.12. Ebola vaccine (rDNA68, replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202009

Applicant(s): Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

### 16.1.13. Etravirine - INTELENCE (CAP) - PSUSA/00001335/202009

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

### 16.1.14. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202010

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

### 16.1.15. Insulin aspart - FIASP (CAP); INSULIN ASPART SANOFI (CAP); NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/00001749/202009

Applicant(s): Novo Nordisk A/S (Fiasp, NovoMix, NovoRapid), Sanofi-aventis groupe (Insulin aspart Sanofi)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

### 16.1.16. Insulin human69 - INSUMAN (CAP) - PSUSA/00010107/202009

Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

### 16.1.17. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202009

Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### 16.1.18. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202009

Applicant: Kyowa Kirin Holdings B.V.

[68] Recombinant deoxyribonucleic acid
[69] Intraperitoneal use only

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### 16.1.19. Netupitant, palonosetron - AKYNZEO (CAP) - PSUSA/00010393/202010

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Evaluation of a PSUSA procedure

### 16.1.20. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202009

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

### 16.1.21. Pitolisant - WAKIX (CAP) - PSUSA/00010490/202009

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

### 16.1.22. Ranibizumab - LUCENTIS (CAP) - PSUSA/00002609/202010

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### 16.1.23. Sofosbuvir, ledipasvir - HARVONI (CAP) - PSUSA/00010306/202010

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

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. Iloprost[70] - VENTAVIS (CAP); NAP - PSUSA/00001724/202009

Applicants: Bayer AG (Ventavis), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

[70] Nebuliser solution(s) only

### 16.2.2. Sodium oxybate[71] - XYREM (CAP); NAP - PSUSA/00010612/202010

Applicants: UCB Pharma S.A. (Xyrem), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

### 16.2.3. Vigabatrin - KIGABEQ (CAP); NAP - PSUSA/00003112/202009

Applicants: Orphelia Pharma SAS (Kigabeq), various

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

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

### 16.3.1. Ambrosia artemisiifolia[72] [73] [74] [75] (NAP) - PSUSA/00010693/202010

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

### 16.3.2. Bivalirudin (NAP) - PSUSA/00000421/202009

Applicant(s): various

PRAC Lead: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

### 16.3.3. Lactitol (NAP) - PSUSA/00001819/202009

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

### 16.3.4. Lisinopril (NAP); lisinopril, hydrochlorothiazide (NAP) - PSUSA/00010532/202009

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

[71] Oral use only
[72] Allergen for therapy
[73] (302)
[74] Sublingual use only
[75] Medicinal product(s) authorised via decentralised procedure

### 16.3.5. Opium (NAP) - PSUSA/00010670/202009

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

### 16.3.6. Podophyllotoxin (NAP) - PSUSA/00002454/202009

Applicant(s): various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

### 16.3.7. Silver sulfadiazine (NAP) - PSUSA/00002702/202009

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

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

### 16.4.1. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/LEG 031.1

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to LEG 031 [cumulative review of cases of acute pancreatitis as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00009204/202001) adopted in September 2020] as per the request for supplementary information (RSI) adopted in January 2021

# 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, 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)[76]

### 17.1.1. Cidofovir (NAP) - EMEA/H/N/PSA/S/0058.1

Applicant: Tillomed Laboratories Ltd. (Cidofovir Emcure Pharma)

PRAC Rapporteur: Rugile Pilviniene

Scope: MAH's response to PSA/S/0058 [substantial amendment to a protocol previously agreed in November 2018 (PSP/S/0052.3) for cidofovir exposure registry study: a non-

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

interventional, prospective, exposure (safety outcome) registry study of cidofovir to further elucidate the characteristics of the different patient populations for cidofovir use, to evaluate patterns and compare rates of adverse events occurring in the on-label group with events occurring in the off-label group; and to assess patient outcome following treatment in specified indication] as per the request for supplementary information (RSI) adopted in October 2020

### 17.1.2. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053.2

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0053.1 [substantial amendment to a protocol previously agreed in March 2018 (PSA/S/0026) for study PARADIGHM (physicians advancing disease knowledge in hypoparathyroidism): a registry for subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism] as per the request for supplementary information (RSI) adopted in November 2020

### 17.1.3. Valproate (NAP) - EMEA/H/N/PSP/J/0072.4

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Progress report for a joint retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)]

### 17.1.4. Valproate (NAP) - EMEA/H/N/PSP/J/0075.4

Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Progress report and substantial amendment to a protocol previously agreed in February 2020 for a joint drug utilisation study (DUS) to assess the effectiveness of the new risk minimisation measures (RMMs) and to further characterise the prescribing patterns for valproate as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454]

## 17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[77]

### 17.2.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 006.4

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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

Scope: MAH's response to MEA 006.3 [MAH's request to discontinue pregnancy registry study OBS13436: an international Lemtrada pregnancy exposure cohort in multiple sclerosis [final clinical study report (CSR) initially expected in December 2021] as per the request for supplementary information (RSI) adopted in October 2020

### 17.2.2. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/MEA 004.2

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed in December 2018 for a non-interventional prospective cohort paediatric study in the treatment of children with X-linked hypophosphataemia (XLH) to assess the long term safety of Crysvita (burosumab) during routine clinical care using data collected in a European disease registry for XLH [final report expected in December 2028]

### 17.2.3. Coronavirus (COVID-19) mRNA[78] vaccine (nucleoside-modified) - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011 [protocol for study C4591010: assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine [final clinical study report (CSR) expected in March 2024] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in March 2021

### 17.2.4. Coronavirus (COVID-19) mRNA[79] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 005.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 005 [protocol for a study (listed as a category 3 study in the RMP): Moderna mRNA-1273 observational pregnancy outcome study to evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine during pregnancy [final clinical study report (CSR) expected in June 2024] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in March 2021

### 17.2.5. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 005

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Protocol for study ZX008-2102: a drug utilisation study (DUS) in Europe to describe fenfluramine use in routine clinical practice [final report expected in August 2025] (from initial opinion/marketing authorisation)

[78] Messenger ribonucleic acid
[79] Messenger ribonucleic acid

### 17.2.6. Fostamatinib - TAVLESSE (CAP) - EMEA/H/C/005012/MEA 002.2

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.1 [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 December 2020

### 17.2.7. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/MEA 006.2

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 006.1 [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 December 2020

### 17.2.8. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 003.1

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Laurence de Fays

Scope: MAH's response to MEA 003 [protocol for study ACE-536-MDS-005 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] as per the request for supplementary information (RSI) adopted in December 2020

### 17.2.9. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 002.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 002.1 [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 December 2020

### 17.2.10. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 004.2

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 004.1 [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 December 2020

### 17.2.11. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 030.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: MAH's response to MEA 030 [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 the Transplant Pregnancy Registry International (TPRI) registry] as per the request for supplementary information (RSI) adopted in December 2020

### 17.2.12. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 022.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 022 [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 the Transplant Pregnancy Registry International (TPRI) registry] as per the request for supplementary information (RSI) adopted in December 2020

## 17.3. Results of PASS imposed in the marketing authorisation(s)[80]

None

## 17.4. Results of PASS non-imposed in the marketing authorisation(s)[81]

### 17.4.1. Epoetin zeta - RETACRIT (CAP) - EMEA/H/C/000872/II/0100

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for study PASCO II (listed as a category 3 study in the RMP): a joint post-authorisation safety observational cohort study of Retacrit/Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anaemia to estimate the incidence of pure red cell aplasia (PRCA), neutralising antibodies, lack of efficacy and thromboembolic events under treatment with Retacrit/Silapo (epoetin zeta). The RMP (version 16.0) is updated accordingly

[80] In accordance with Article 107p-q of Directive 2001/83/EC
[81] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 04 August 2013

### 17.4.2. Epoetin zeta - SILAPO (CAP) - EMEA/H/C/000760/II/0062

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Martin Huber

Scope: Submission of the final study report for study PASCO II (listed as a category 3 study in the RMP): a joint post-authorisation safety observational cohort study of Retacrit/Silapo (epoetin zeta) administered subcutaneously for the treatment of renal anaemia to estimate the incidence of pure red cell aplasia (PRCA), neutralising antibodies, lack of efficacy and thromboembolic events under treatment with Retacrit/Silapo (epoetin zeta). The RMP (version 12.0) is updated accordingly

### 17.4.3. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/WS1653/0230; LIFMIOR[82] - EMEA/H/C/004167/WS1653/0024

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): 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. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/II/0034

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final study report for study SOFIA (listed as a category 3 study in the RMP): a phase 4, multinational, comparative, prospective, non-interventional, observational cohort study evaluating the safety of Ovaleap (follitropin alfa) in infertile women undergoing superovulation for assisted reproductive technologies. The RMP (version 3.3) is updated accordingly

### 17.4.5. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0032

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final clinical study report (CSR) for study AMDC-204-401: a post-authorisation observational study to evaluate the safety of Adasuve (loxapine for inhalation) in agitated persons in routine clinical care (EU PASS). The RMP (version 9.3) is updated accordingly

### 17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0044

Applicant: Amgen Europe B.V., ATMP[83]

[82] Marketing authorisation(s) ceased to be valid in the European Union (EU) on 16 February 2020
[83] Advanced therapy medicinal product

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study 20180099 (listed as a category 3 study in the RMP): a cross-sectional survey to evaluate physician knowledge of safety messages included in the physician education booklet (PEB) for Imlygic (talimogene laherparepvec)

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

### 17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.11

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Sixth annual progress report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long-term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)

### 17.5.2. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019.6

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 019.5 [second interim report for drug utilisation survey OBS14697: a drug utilisation study to assess the effectiveness of dosing recommendation of Praluent (alirocumab) as per the product information to avoid very low-density lipoprotein (LDL)-C levels [final results expected in Q3 2021]] as per the request for supplementary information (RSI) adopted in January 2021

### 17.5.3. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/MEA 002.3

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second yearly progress update report for study MS100070-0031 (listed as a category 3 study in the RMP): a non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany [final study report expected in Q1/2024]

### 17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.2

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Eleventh annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

### 17.5.5. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.9

Applicant: Hexal AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.8 [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 December 2020

### 17.5.6. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.9

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.8 [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 December 2020

### 17.5.7. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/002789/ANX 004.5

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Third annual interim report for a post-marketing, open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection, using data collected through European cystic fibrosis registries [final clinical study report (CSR) expected in June 2022]

### 17.5.8. Lutetium ($^{177}$Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.6

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Quarterly progress report for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium ($^{177}$Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) [final clinical study report (CSR) expected in December 2025]

### 17.5.9. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.9

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Eleventh annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

### 17.5.10. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.3

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Eleventh annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]

### 17.5.11. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.3

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: First study progress report for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final clinical study report (CSR) expected in Q3 2025]

### 17.5.12. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.22

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Tenth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics

## 17.6. Others

### 17.6.1. Coronavirus (COVID-19) mRNA[84] vaccine (nucleoside-modified) - COVID-19 VACCINE MODERNA (CAP) - EMEA/H/C/005791/MEA 004.1

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Hans Christian Siersted

Scope: MAH's response to MEA 004 [feasibility assessment for a study (listed as a category 3 study in the RMP): a post-authorisation active surveillance safety study using secondary data to monitor real-world safety of the mRNA-1273 Vaccine in the EU - an enhanced pharmacovigilance study to provide additional evaluation of adverse events of special interest (AESI) and emerging validated safety signals in European populations; Electronic database assessment of use in pregnant women) [final clinical study report (CSR) expected

[84] Messenger ribonucleic acid

in December 2023] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in March 2021

### 17.6.2. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/ANX 004.4

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to ANX 004.3 [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] as per the request for supplementary information (RSI) adopted in December 2020

### 17.6.3. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003.9

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 003.8 [second feasibility assessment report for study NB-451: an observational retrospective study based on secondary data analysis using existing databases, in order to evaluate the potential population of patients or prescriptions in each database and confirm the ability to use each database for the drug utilisation study (DUS) of Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in selected European countries to describe the demographic and baseline characteristics of users of Mysimba (naltrexone hydrochloride/bupropion hydrochloride)] as per the request for supplementary information (RSI) adopted in October 2020

## 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, 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 PRAC level without further plenary discussion.

## 18.1. Annual reassessments of the marketing authorisation

### 18.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0035 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

## 18.2. Conditional renewals of the marketing authorisation

### 18.2.1. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/R/0007 (without RMP)

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### 18.2.2. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0003 (without RMP)

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

### 18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0014 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Conditional renewal of the marketing authorisation

## 18.3. Renewals of the marketing authorisation

### 18.3.1. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/R/0071 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

### 18.3.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/R/0039 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

### 18.3.3. Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004137/R/0019 (without RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

### 18.3.4. Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/R/0028 (with RMP)

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

### 18.3.5. Irinotecan hydrochloride trihydrate - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/004125/R/0025 (without RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: 5-year renewal of the marketing authorisation

### 18.3.6. Ivabradine - IVABRADINE ZENTIVA (CAP) - EMEA/H/C/004117/R/0008 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

### 18.3.7. Palbociclib - IBRANCE (CAP) - EMEA/H/C/003853/R/0034 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

### 18.3.8. Sildenafil - MYSILDECARD (CAP) - EMEA/H/C/004186/R/0009 (without RMP)

Applicant: Mylan S.A.S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

### 18.3.9. Tenofovir disoproxil - TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004120/R/0023 (without RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Adrien Inoubli

Scope: 5-year renewal of the marketing authorisation

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 03-06 May 2021 meeting (marked as "a"), and for the 20 May 2021 ORGAM teleconference (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 [a, b] | Chair | The Netherlands | No interests declared | Full involvement |
| Jan Neuhauser [a, b] | Member | Austria | No interests declared | Full involvement |
| Sonja Hrabcik [a] | Alternate | Austria | No interests declared | Full involvement |
| Jean-Michel Dogné [a, b] | Member | Belgium | No interests declared | Full involvement |
| Laurence de Fays [a, b] | Alternate | Belgium | No interests declared | Full involvement |
| Maria Popova-Kiradjieva [a, b] | Member | Bulgaria | No interests declared | Full involvement |
| Nikica Mirošević Skvrce [a, b] | Member | Croatia | No interests declared | Full involvement |
| Christina Sylvia Chrysostomou [a, b] | Alternate | Cyprus | No interests declared | Full involvement |
| Panagiotis Psaras [a, b] | Member | Cyprus | No interests declared | Full involvement |
| Eva Jirsová [a, b] | Member | Czechia | No interests declared | Full involvement |
| Jana Lukacisinova [a] | Alternate | Czechia | No interests declared | Full involvement |
| Anette Stark [a, b] | Member | Denmark | No interests declared | Full involvement |
| Hans Christian Siersted [a, b] | Alternate | Denmark | No restrictions | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | applicable to this meeting | |
| Maia Uusküla [a, b] | Member | Estonia | No interests declared | Full involvement |
| Kirsti Villikka [a, b] | Member | Finland | No interests declared | Full involvement |
| Kimmo Jaakkola [a, b] | Alternate | Finland | No interests declared | Full involvement |
| Adrien Inoubli [a, b] | Member | France | No interests declared | Full involvement |
| Tiphaine Vaillant [a, b] | Alternate | France | No interests declared | Full involvement |
| Martin Huber [a, b] | Member (Vice-Chair) | Germany | No interests declared | Full involvement |
| Brigitte Keller-Stanislawski [a] | Alternate | Germany | No interests declared | Full involvement |
| Agni Kapou [a, b] | Member | Greece | No interests declared | Full involvement |
| Julia Pallos [a, b] | Member | Hungary | No participation in final deliberations and voting on: | 4.3.13. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP) 4.3.14. Sulfamethoxazole, trimethoprim (co-trimoxazole) (NAP) 4.3.15. Tramadol; tramadol, dexketoprofen; tramadol, paracetamol (NAP) |
| Melinda Palfi [a] | Alternate | Hungary | No interests declared | Full involvement |
| Guðrún Stefánsdóttir [a, b] | Member | Iceland | No participation in discussion, | 15.3.3. Blinatumomab - BLINCYTO (CAP) - |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | final deliberations and voting on: | II/0038, 16.1.20. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202009, 17.2.11. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 030.1, 7.2.12. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 022.1, 17.4.6. Talimogene laherparepvec - IMLYGIC (CAP) - II/0044 |
| Rhea Fitzgerald [a, b] | Member | Ireland | No interests declared | Full involvement |
| Amelia Cupelli [a, b] | Member | Italy | No interests declared | Full involvement |
| Ilaria Baldelli [a, b] | Alternate | Italy | No interests declared | Full involvement |
| Zane Neikena [a, b] | Member | Latvia | No interests declared | Full involvement |
| Rugile Pilviniene [a, b] | Member | Lithuania | No interests declared | Full involvement |
| Anne-Cécile Vuillemin [a, b] | Alternate | Luxembourg | No interests declared | Full involvement |
| John Joseph Borg [a] | Member (CHMP member) | Malta | No interests declared | Full involvement |
| Menno van der Elst [a, b] | Member | The Netherlands | No interests declared | Full involvement |
| Liana Gross-Martirosyan [a, b] | Alternate | The Netherlands | 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 |
|---|---|---|---|---|
| David Olsen [a, b] | Member | Norway | No participation in final deliberations and voting on: | 4.3.15. Tramadol; tramadol, dexketoprofen; tramadol, paracetamol (NAP), 5.1.4 Coronavirus (COVID-19) mRNA vaccine - EMEA/H/C/005845, 16.2.1. Iloprost - VENTAVIS (CAP); NAP - PSUSA/00001724/202009, 17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.2, 17.5.9. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.9, 17.5.10. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.3, 18.2.3. Larotrectinib - VITRAKVI (CAP) - EMEA/H/C/004919/R/0014 (without RMP) |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Karen Pernille Harg [a, b] | Alternate | Norway | No interests declared | Full involvement |
| Katarzyna Ziolkowska [a, b] | Alternate | Poland | No interests declared | Full involvement |
| Ana Diniz Martins [a, b] | Member | Portugal | No interests declared | Full involvement |
| Marcia Silva [a, b] | Alternate | Portugal | No interests declared | Full involvement |
| Roxana Dondera [a, b] | Member | Romania | No interests declared | Full involvement |
| Alexandra - Maria Spurni [a, b] | Alternate | Romania | No interests declared | Full involvement |
| Michal Radik [a, b] | Member | Slovakia | No interests declared | Full involvement |
| Marek Juracka [a] | Alternate | Slovakia | No interests declared | Full involvement |
| Jasmina Klopcic [a, b] | Alternate | Slovenia | No interests declared | Full involvement |
| Eva Segovia [a, b] | Member | Spain | No interests declared | Full involvement |
| Maria del Pilar Rayon [a, b] | Alternate | Spain | No interests declared | Full involvement |
| Ulla Wändel Liminga [a, b] | Member | Sweden | No interests declared | Full involvement |
| Annika Folin [a, b] | Alternate | Sweden | No interests declared | Full involvement |
| Birgitta Grundmark [a] | Member | Independent scientific expert | No interests declared | Full involvement |
| Daniel Morales [a] | Member | Independent scientific expert | No interests declared | Full involvement |
| Hedvig Nordeng [a] | Member | Independent scientific expert | No interests declared | Full involvement |
| Antoine Pariente [a] | Member | Independent scientific expert | No participation in final deliberations and voting on: | 15.2.8. Obeticholic acid - OCALIVA (CAP) - II/0026 |
| Milou Daniel Drici [a, b] | Member | Independent scientific expert | No restrictions applicable to this meeting | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Stefan Weiler [a] | Member | Independent scientific expert | No interests declared | Full involvement |
| Raymond Anderson [a] | Member | Healthcare Professionals' Representative | No interests declared | Full involvement |
| Roberto Frontini [a, b] | Alternate | Healthcare Professionals' Representative | No restrictions applicable to this meeting | Full involvement |
| Cathalijne van Doorne [a, b] | Member | Patients' Organisation Representative | No interests declared | Full involvement |
| Virginie Hivert [a] | Alternate | Patients' Organisation Representative | No restrictions applicable to this meeting | Full involvement |
| Els Beghein [a] | Expert - via telephone* | Belgium | No interests declared | Full involvement |
| Christelle Bizimungu [a, b] | Expert - via telephone* | Belgium | No restrictions applicable to this meeting | Full involvement |
| Inne Crevecoeur [a, b] | Expert - via telephone* | Belgium | No restrictions applicable to this meeting | Full involvement |
| Evelien De Clercq [a, b] | Expert - via telephone* | Belgium | No restrictions applicable to this meeting | Full involvement |
| Jamila Hamdani [a, b] | Expert - via telephone* | Belgium | No interests declared | Full involvement |
| Martine Sabbe [a, b] | Expert - via telephone* | Belgium | No interests declared | Full involvement |
| Charlotte Selvais [a] | Expert - via telephone* | Belgium | No interests declared | Full involvement |
| Françoise Wuillaume [a, b] | Expert - via telephone* | Belgium | No interests declared | Full involvement |
| Ivana Ljubičić [a] | Expert - via telephone* | Croatia | No restrictions applicable to this meeting | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Petra Kaftanová [a, b] | Expert - via telephone* | Chechia | No interests declared | Full involvement |
| Kristýna Schneiderová [a] | Expert - via telephone* | Chechia | No interests declared | Full involvement |
| Petra Vacková [b] | Expert - via telephone* | Chechia | No interests declared | Full involvement |
| Karin Erneholm [a] | Expert - via telephone* | Denmark | No restrictions applicable to this meeting | Full involvement |
| Helle Esbjørn Kristensen [a] | Expert - via telephone* | Denmark | No interests declared | Full involvement |
| Kristina Laursen [a] | Expert - via telephone* | Denmark | No interests declared | Full involvement |
| Emma Louise Nautrup Ravn Stadsbjerg [a] | Expert - via telephone* | Denmark | No interests declared | Full involvement |
| Josiane Uwera [a] | Expert - via telephone* | Denmark | No interests declared | Full involvement |
| Päivi Susanna Worsøe [a] | Expert - via telephone* | Denmark | No interests declared | Full involvement |
| Krõõt Aab [a] | Expert - via telephone* | Estonia | No interests declared | Full involvement |
| Hanna Leskinen [b] | Expert - via telephone* | Finland | No interests declared | Full involvement |
| Karima Adamo [a] | Expert - via telephone* | France | No restrictions applicable to this meeting | Full involvement |
| Alice Aribaud [a] | Expert - via telephone* | France | No interests declared | Full involvement |
| Emmanuel Doyen [a] | Expert - via telephone* | France | No interests declared | Full involvement |
| Leo Lambart [a] | Expert - via telephone* | France | No restrictions applicable to this meeting | Full involvement |
| Alexis Jacquet [a] | Expert - via telephone* | France | No restrictions applicable to this meeting | Full involvement |
| Youssef Shaim [a] | Expert - via telephone* | France | No restrictions | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| | | | applicable to this meeting | |
| Dennis Lex [a, b] | Expert - via telephone* | Germany | No restrictions applicable to this meeting | Full involvement |
| Nerina Pflanz [a] | Expert - via telephone* | Germany | No interests declared | Full involvement |
| Grainne Kirwan [a] | Expert - via telephone* | Ireland | No interests declared | Full involvement |
| Gintare Gilaite [a] | Expert - via telephone* | Lithuania | No interests declared | Full involvement |
| Petra Brina Kovačič [b] | Expert - via telephone* | Slovenia | No interests declared | Full involvement |
| Polona Golmajer [a] | Expert - via telephone* | Slovenia | No interests declared | Full involvement |
| Ana Fernández Dueñas [a] | Expert - via telephone* | Spain | No interests declared | Full involvement |
| Verónica García Gil [a] | Expert - via telephone* | Spain | No interests declared | Full involvement |
| Nuria Garcia Sainz [a] | Expert - via telephone* | Spain | No interests declared | Full involvement |
| María Martínez González [a] | Expert - via telephone* | Spain | No restrictions applicable to this meeting | Full involvement |
| Mónica Martínez Redondo [a] | Expert - via telephone* | Spain | No restrictions applicable to this meeting | Full involvement |
| Consuelo Mejías Pavón [a] | Expert - via telephone* | Spain | No interests declared | Full involvement |
| Helena Back [a] | Expert - via telephone* | Sweden | No interests declared | Full involvement |
| Charlotte Backman [a, b] | Expert - via telephone* | Sweden | No interests declared | Full involvement |
| Karin Bolin [a] | Expert - via telephone* | Sweden | No restrictions applicable to this meeting | Full involvement |
| Sofia Bosdotter Enroth [a] | Expert - via telephone* | Sweden | No interests declared | Full involvement |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Rolf Gedeborg [a] | Expert - via telephone* | Sweden | No restrictions applicable to this meeting | Full involvement |
| Erika Gustafsson [a] | 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 evaluated against the agenda topics or activities they participated in

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

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

## 21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

### Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action

may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

### Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

### Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

### Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website: https://www.ema.europa.eu/en