



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for medicinal products for human use (CHMP)

Minutes of CHMP written procedure* 19-22 August 2019

Chair: Harald Enzmann – Vice-Chair: Bruno Sepodes

*** Written Procedure - comments on the draft documents should be forwarded to the Product Lead (PL) as identified in the CHMP agenda.**

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review.

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

Note on access to documents

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



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1. Introduction

1.1. Adoption of agenda

CHMP agenda for 19-22 August 2019

The CHMP adopted the agenda.

1.2. Adoption of the minutes

The CHMP minutes from the 22-25 July 2019 meeting will be adopted at the September CHMP plenary on 16–19 September 2019.

2. Oral Explanations

No items

3. Initial applications

3.1. Initial applications; Opinions

No items

3.2. Initial applications; List of outstanding issues (Day 180; Day 120 for procedures with accelerated assessment timetable)

No items

3.3. Initial applications; List of questions (Day 120; Day 90 for procedures with accelerated assessment timetable)

No items

3.4. Update on on-going initial applications for Centralised procedure

3.4.1. emapalumab - Orphan - EMEA/H/C/004386

Novimmune B.V.; treatment of paediatric patients with primary haemophagocytic lymphohistiocytosis (HLH).

Scope: Letter from applicant dated 26 July 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted in June 2019



Action: For adoption

List of Outstanding Issues adopted on 27.06.2019. List of Questions adopted on 13.12.2018.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the list of outstanding issues adopted on 27.06.2019.

3.4.2. [ciprofloxacin - EMEA/H/C/004394](#)

treatment of non-cystic fibrosis bronchiectasis (NCFBE) patients with chronic lung infection with *Pseudomonas aeruginosa* (*P. aeruginosa*)

Scope: Letter from applicant dated 06 August 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted in March 2019

Adopted via written procedure on 14.08.2019

Action: For information

List of Outstanding Issues adopted on 28.03.2019. List of Questions adopted on 26.07.2018.

The CHMP noted the request by the applicant for an extension to the clock stop to respond to the list of outstanding issues adopted on 28.03.2019, which was adopted via written procedure on 14.08.2019

3.4.3. [esketamine - EMEA/H/C/004535](#)

treatment-resistant depression

Scope: Communication from applicant dated 16 August 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted in July 2019

Action: For adoption

List of Outstanding Issues adopted on 25.07.2019. List of Questions adopted on 28.02.2019.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the list of outstanding issues adopted on 25.07.2019

3.4.4. [plazomicin - EMEA/H/C/004457](#)

treatment of complicated urinary tract infection (cUTI), including pyelonephritis; treatment of bloodstream infection (BSI); treatment of infections due to Enterobacteriaceae

Scope: Letter from applicant dated 30 July 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted in July 2019

Action: For adoption

List of Outstanding Issues adopted on 25.07.2019. List of Questions adopted on 28.02.2019.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the list of outstanding issues adopted on 25.07.2019

3.5. Re-examination of initial application procedures under Article 9(2) of Regulation no 726/2004

No items

3.6. Initial applications in the decision-making phase

No items

3.7. Withdrawals of initial marketing authorisation application

No items

4. Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008

4.1. Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Opinion

No items

4.2. Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Day 180 list of outstanding issues

No items

4.3. Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Day 120 List of question

No items

4.4. Update on on-going extension application according to Annex I of Commission Regulation (EC) No 1234/2008

No items

4.5. Re-examination procedure of extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008

No items

5. Type II variations - variation of therapeutic indication procedure according to Annex I of Commission Regulation (EC) No 1234/2008

5.1. Type II variations - variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008; Opinions or Requests for supplementary information

No items

5.2. Update on on-going Type II variation; variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008

No items

5.3. Re-examination of Type II variation; variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008

No items

6. Ancillary medicinal substances in medical devices

6.1. Ancillary medicinal substances in medical devices; Opinions/ Day 180 list of outstanding issues / Day 120 list of questions

No items

6.2. Update of Ancillary medicinal substances in medical devices

No items

7. Procedure under Article 83(1) of Regulation (EC) 726/2004 (Compassionate Use)

7.1. Procedure under Article 83(1) of Regulation (EC) 726/2004 (Compassionate Use)

No items

8. Pre-submission issues

8.1. Pre-submission issue

No items

8.2. Priority Medicines (PRIME)

Disclosure of information related to priority medicines cannot be released at present time as these contain commercially confidential information

No items

9. Post-authorisation issues

9.1. Post-authorisation issues

9.1.1. Cerdelga - eliglustat – Orphan - EMEA/H/C/003724/R/0022

Genzyme Europe BV

Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Martina Weise, PRAC Rapporteur: Eva A. Segovia

Scope: Request by the applicant for an extension to the clock stop to respond to the request for supplementary information adopted on 25.07.2019

Action: For adoption

Request for Supplementary Information adopted on 25.07.2019.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the request for supplementary information adopted on 25.07.2019

10. Referral procedures

10.1. Procedure for Centrally Authorised products under Article 20 of Regulation (EC) No 726/2004

No items

10.2. Requests for CHMP Opinion under Article 5(3) of Regulation (EC) No 726/2004

No items

10.3. Procedure under Articles 5(2) and 10 of Regulation (EC) No 726/2004

No items

10.4. Disagreement between Member States on application for medicinal product (potential serious risk to public health) –under Article 29(4) of Directive 2001/83/EC

No items

10.5. Harmonisation - Referral procedure under Article 30 of Directive 2001/83/EC

No items

10.6. Community Interests - Referral under Article 31 of Directive 2001/83/EC

10.6.1. Gadolinium-containing contrast agents (GdCA): Gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP) - EMEA/H/A-31/1097

Applicant: various

Lead Rapporteur: Johann Lodewijk Hillege (NL)

Scope: Annual cumulative reviews on NSF cases submission as a post-authorisation measure resulting from the 2010 Article 20 and Article 31 referral procedures for gadolinium-containing contrast agents

Timetable

Action: For adoption

The CHMP adopted the procedure timetable.

10.6.2. Methotrexate - JYLAMVO (CAP), NORDIMET (CAP); NAP - EMEA/H/A-31/1463

Applicants: Nordic Group B.V. (Nordimet), Therakind Limited (Jylamvo), various

Referral PRAC Rapporteur: Martin Huber; Referral PRAC Co-rapporteur: Željana Margan Koletić

Jylamvo EMEA/H/C/003756 - Rapporteur: Bruno Sepodes, PRAC Rapporteur: Jan Neuhauser

Nordimet EMEA/H/C/003983 - Rapporteur: Bruno Sepodes, PRAC Rapporteur: Martin Huber

Scope: CHMP opinion

Action: For adoption

Review of the benefit-risk balance following notification by Spain of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

The procedure was discussed at the July 2019 CHMP Plenary meeting.

Based on the PRAC recommendation, the CHMP adopted an opinion by consensus, recommending that the marketing authorisations for methotrexate-containing medicinal products should be varied.

The Committee considered that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Icelandic and Norwegian Members were in agreement with the CHMP recommendation.

10.7. Re-examination Procedure under Article 32(4) of Directive 2001/83/EC

No items

10.8. Procedure under Article 107(2) of Directive 2001/83/EC

No items

10.9. Disagreement between Member States on Type II variation– Arbitration procedure initiated by MAH under Article 6(13) of Commission Regulation (EC) No 1084/2003

No items

10.10. Procedure under Article 29 of Regulation (EC) 1901/2006

No items

10.11. Referral under Article 13 Disagreement between Member States on Type II variation– Arbitration procedure initiated by Member State under Article 13 (EC) of Commission Regulation No 1234/2008

No items

11. Pharmacovigilance issue

11.1. Early Notification System

August 2019 Early Notification System on envisaged CHMP/CMDh outcome accompanied by communication to the general public.

Action: For information

12. Inspections

12.1. GMP inspections

Information related to GMP inspections will not be published as it undermines the purpose of such inspections

12.2. GCP inspections

Information related to GCP inspections will not be published as it undermines the purpose of such inspections

12.3. Pharmacovigilance inspections

Information related to Pharmacovigilance inspections will not be published as it undermines the purpose of such inspections

12.4. GLP inspections

Information related to GLP inspections will not be published as it undermines the purpose of such inspections

13. Innovation Task Force

13.1. Minutes of Innovation Task Force

Action: For information

13.2. Innovation Task Force briefing meetings

Information related to briefing meetings taking place with applicants cannot be released at the present time as it is deemed to contain commercially confidential information

No items

13.3. Requests for CHMP Opinion under Article 57(1)J and (1)P of Regulation (EC) No 726/2004

No items

13.4. Nanomedicines activities

No items

14. Organisational, regulatory and methodological matters

14.1. Mandate and organisation of the CHMP

No items

14.2. Coordination with EMA Scientific Committees

No items

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

No items

14.4. Cooperation within the EU regulatory network

No items

14.5. Cooperation with International Regulators

No items

14.6. Contacts of the CHMP with external parties and interaction with the Interested Parties to the Committee

No items

14.7. CHMP work plan

No items

14.8. Planning and reporting

No items

14.9. Others

No items

15. Any other business

15.1. AOB topic

No items

A. PRE SUBMISSION ISSUES

A.1. ELIGIBILITY REQUESTS

No items

A.2. Appointment of Rapporteur / Co-Rapporteur Full Applications

No items

A.3. PRE-SUBMISSION ISSUES FOR INFORMATION

Information related to pre-submission of initial applications cannot be released at the present time as these contain commercially confidential information.

B. POST-AUTHORISATION PROCEDURES OUTCOMES

B.1. Annual re-assessment outcomes

B.1.1. Annual reassessment for products authorised under exceptional circumstances

B.2. RENEWALS OF MARKETING AUTHORISATIONS OUTCOMES

B.2.1. Renewals of Marketing Authorisations requiring 2nd Renewal

B.2.2. Renewals of Marketing Authorisations for unlimited validity

B.2.3. Renewals of Conditional Marketing Authorisations

B.3. POST-AUTHORISATION PHARMACOVIGILANCE OUTCOMES

B.4. EPARs / WPARs

Deferasirox Mylan - deferasirox - EMA/H/C/005014

Mylan S.A.S, treatment of chronic iron overload,
Generic, Generic of EXJADE, Generic application
(Article 10(1) of Directive No 2001/83/EC)

For information only. Comments can be sent to
the PL in case necessary.

Epidyolex - cannabidiol - EMA/H/C/004675, Orphan

GW Pharma (International) B.V., Adjunctive
therapy of seizures associated with
Lennox-Gastaut syndrome (LGS) or Dravet
syndrome (DS), New active substance (Article
8(3) of Directive No 2001/83/EC)

For information only. Comments can be sent to
the PL in case necessary.

Inbrija - levodopa - EMA/H/C/004786

Acorda Therapeutics Ireland Limited, treatment
of symptoms of OFF periods in Parkinson's
disease, Known active substance (Article 8(3) of
Directive No 2001/83/EC)

For information only. Comments can be sent to
the PL in case necessary.

<p>Nuceiva - botulinum toxin type a - EMEA/H/C/004587</p> <p>Evolus Pharma Limited, temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows, New active substance (Article 8(3) of Directive No 2001/83/EC)</p>	<p>For information only. Comments can be sent to the PL in case necessary.</p>
<p>Trogarzo - ibalizumab - EMEA/H/C/004961</p> <p>Theratechnologies International Limited, treatment of adults infected with HIV-1 resistant to at least 1 agent in 3 different classes, New active substance (Article 8(3) of Directive No 2001/83/EC)</p>	<p>For information only. Comments can be sent to the PL in case necessary.</p>
<p>VITRAKVI - larotrectinib - EMEA/H/C/004919, Orphan</p> <p>Bayer AG, treatment of adult and paediatric patients with locally advanced or metastatic solid tumours, New active substance (Article 8(3) of Directive No 2001/83/EC)</p>	<p>For information only. Comments can be sent to the PL in case necessary.</p>

B.5. TYPE II VARIATION, WORKSHARING PROCEDURE OUTCOMES

Scopes related to Chemistry, Manufacturing, and Controls cannot be released at the present time as these contain commercially confidential information.

B.5.1. CHMP assessed procedures scope: Pharmaceutical aspects

<p>Flucelvax Tetra - influenza vaccine surface antigen inactivated prepared in cell cultures - EMEA/H/C/004814/II/0007</p> <p>Seqirus Netherlands B.V., Rapporteur: Sol Ruiz</p> <p>Opinion adopted on 09.08.2019.</p> <p>Request for Supplementary Information adopted on 25.07.2019.</p>	<p>Positive Opinion adopted by consensus on 09.08.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Fluenz Tetra - influenza vaccine (live attenuated, nasal) - EMEA/H/C/002617/II/0093</p> <p>AstraZeneca AB, Rapporteur: Bart Van der Schueren</p> <p>Opinion adopted on 09.08.2019.</p> <p>Request for Supplementary Information adopted on 25.07.2019.</p>	<p>Positive Opinion adopted by consensus on 09.08.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>

B.5.2. CHMP assessed procedures scope: Non-Clinical and Clinical aspects

B.5.3. CHMP-PRAC assessed procedures

B.5.4. PRAC assessed procedures

B.5.5. CHMP-CAT assessed procedures

B.5.6. CHMP-PRAC-CAT assessed procedures

B.5.7. PRAC assessed ATMP procedures

B.5.8. Unclassified procedures and worksharing procedures of type I variations

B.5.9. Information on withdrawn type II variation / WS procedure

Kyprolis - carfilzomib -

The MAH withdrew the procedure on 02.08.2019.

EMA/H/C/003790/II/0031, Orphan

Amgen Europe B.V., Rapporteur: Jorge Camarero Jiménez, "Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 to add a once-weekly dose regimen for carfilzomib (Kyprolis) at 20/70 mg/m² in combination with dexamethasone (Kd) for the treatment of the currently indicated patient population. The MAH took the opportunity to implement editorial changes to the SmPC and Patient Information Leaflet (PIL) due to the revised excipients guideline (EMA/CHMP/302620/2017). The PIL is updated accordingly."

Request for Supplementary Information adopted on 27.06.2019, 28.02.2019, 15.11.2018.

Withdrawal request submitted on 02.08.2019.

B.5.10. Information on type II variation / WS procedure with revised timetable

NovoSeven - eptacog alfa (activated) -

The CHMP agreed to the request for an extension to the clock stop to respond to the Request for Supplementary Information adopted on 06.06.2019

EMA/H/C/000074/II/0106

Novo Nordisk A/S, Rapporteur: Paula Boudewina van Hennik

Request for Supplementary Information adopted on 06.06.2019, 07.03.2019, 20.09.2018.

B.6. START OF THE PROCEDURES TIMETABLES FOR INFORMATION

B.6.1. Start of procedure for New Applications: timetables for information

arsenic trioxide - EMA/H/C/005218

treatment of relapsed acute promyelocytic leukaemia (APL)

fampridine - EMA/H/C/005359

treatment of Multiple Sclerosis

filgotinib - EMEA/H/C/005113

treatment of adult patients with moderately to severely active rheumatoid arthritis

budesonide / formoterol fumarate

dihydrate - EMEA/H/C/004882

treatment of asthma and COPD

pegfilgrastim - EMEA/H/C/005312

treatment of neutropenia

rilpivirine - EMEA/H/C/005060

treatment of human of human immunodeficiency virus type 1 (HIV-1)

rivaroxaban - EMEA/H/C/005279

prevention of atherothrombotic events

cabotegravir - EMEA/H/C/004976

treatment of Human Immunodeficiency Virus type 1 (HIV-1)

B.6.2. Start of procedure for Extension application according to Annex I of Reg. 1234/2008): timetables for information

Darzalex - daratumumab -

EMEA/H/C/004077/X/0032, Orphan

Janssen-Cilag International NV, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva, "Extension application to introduce a new pharmaceutical form (solution for injection), a new strength (1800 mg) and a new route of administration (subcutaneous route). The RMP version 7.0 was updated in accordance."

Jorveza - budesonide -

EMEA/H/C/004655/X/0007/G, Orphan

Dr. Falk Pharma GmbH, Rapporteur: Martina Weise, Co-Rapporteur: Tomas Boran, PRAC Rapporteur: Zane Neikena, "Extension application to add a new strength of 0.5 mg for budesonide orodispersible tablets, grouped with:
- A type II variation (C.I.6) - Extension of indication to include the maintenance of remission for Jorveza (0.5 mg and 1 mg orodispersible tablets); as a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated to reflect the recommended daily dose and duration of treatment of Jorveza for the maintenance of remission, to update the list of

adverse reactions and the clinical efficacy and safety information based on the results of the phase III clinical study BUL-2/EER. The relevant sections of the PL are updated accordingly. In addition, a revised RMP (version 2.0) has been submitted to reflect the results of this study and to align with the GVP Module V (rev 2) template. The MAH also took the opportunity to bring the product information in line with the latest QRD template (version 10.1).

- A type IB variation (B.II.e.5.a.2) – To add a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza 1 mg orodispersible tablet (EU/1/17/1254/006)“

B.6.3. Restart of procedure - responses received to Day 120 List of Questions timetables: for information

adalimumab - EMEA/H/C/004879

treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis, paediatric uveitis, adolescent hidradenitis suppurativa

List of Questions adopted on 28.03.2019.

azacitidine - EMEA/H/C/005147

Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) and AML with >30% marrow blasts according to the WHO classification

List of Questions adopted on 29.05.2019.

azacitidine - EMEA/H/C/005075

Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML)

List of Questions adopted on 29.05.2019.

brolocizumab - EMEA/H/C/004913

treatment of neovascular (wet) age-related macular degeneration (AMD)

List of Questions adopted on 27.06.2019.

cinacalcet - EMEA/H/C/005236

treatment of secondary hyperparathyroidism and hypercalcaemia

List of Questions adopted on 29.05.2019.

Dificlir - fidaxomicin -**EMA/H/C/002087/X/0034/G**

Astellas Pharma Europe B.V., Rapporteur: Filip Josephson, PRAC Rapporteur: Ulla Wändel Liminga, "Extension application to introduce a new pharmaceutical form associated with new strength (40 mg/ml granules for oral suspension) grouped with a type II variation (C.I.6.a) to include paediatric use of Dificlir in children from birth to less than 18 years of age.

The RMP (version 11.0) is updated in accordance. Consequential updates have been made to the SmPC of Dificlir 200 mg Film-coated tablet. The labelling and package leaflet (PL) are updated accordingly.

The PL is also being amended to include a statement that Dificlir is essentially 'sodium-free' (in accordance with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'). The details of the local representative of the MAH in the Czech Republic are also updated."

List of Questions adopted on 29.05.2019.

Emgality - galcanezumab -**EMA/H/C/004648/X/0004**

Eli Lilly Nederland B.V., Rapporteur: Daniela Melchiorri (IT) (MNAT with IT for Clinical Pharmacology, IT for Clinical Safety, IT for Clinical Efficacy, IT for Non-Clinical, IT for Coordination, ES for Quality), Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Kirsti Villikka, "Extension application to add a new strength of 100 mg/ml solution for injection in pre-filled syringe for Emgality, associated with a new indication (episodic cluster headache)."

List of Questions adopted on 27.06.2019.

Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

entrectinib - EMA/H/C/004936

treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours and treatment of patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC)

List of Questions adopted on 29.05.2019.

**recombinant vesicular stomatitis virus -
zaire ebolavirus vaccine (live) -
EMA/H/C/004554**

Ebola Vaccine

List of Questions adopted on 25.06.2019.

**imipenem / cilastatin / relebactam -
EMA/H/C/004808**

indicated for the treatment of bacterial infections
due to gram-negative microorganisms

List of Questions adopted on 28.03.2019.

lidocaine / prilocaine - EMA/H/C/005298

treatment of primary premature ejaculation

List of Questions adopted on 25.07.2019.

cholera vaccine, oral, live -

EMA/H/C/003876

indicated for active immunisation against disease
caused by *Vibrio cholerae* serogroup O1 in adults
and children aged 6 years and older

List of Questions adopted on 29.05.2019.

Vyndaqel - tafamidis -

EMA/H/C/002294/X/0049/G, Orphan

Pfizer Europe MA EEIG, Rapporteur: Joseph
Emmerich, Co-Rapporteur: Bruno Sepodes, PRAC
Rapporteur: Ghania Chamouni, "Extension
application to:

- introduce a new strength (tafamidis 61 mg soft capsules, pack-size of 30 and 90 capsules) including a new indication "treatment of transthyretin amyloidosis in adult patients with wild-type or hereditary cardiomyopathy to reduce all-cause mortality and cardiovascular-related hospitalisation (ATTR-CM)"

- introduce qualitative change in declared active substance (tafamidis) not defined as a new active substance;

grouped with a type II variation (C.I.4) to update section 4.6 of the Vyndaqel (tafamidis meglumine) 20 mg soft capsules SmPC to add wording pertaining to the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) programme.

Submission of an updated RMP version 9.0 in order to include the proposed new dosage/indication, review of the additional data collected from the ATTR-CM clinical program and post marketing reporting, reclassify of the safety concerns, remove of HCP educational leaflet.

Relevant changes are proposed for Annex II.

In addition, the MAH is proposing an update to section 16 Information in Braille of Annex IIIa - Labelling (carton) to differentiate between the dosage forms.)”

List of Questions adopted on 29.05.2019.

Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

B.6.4. Annual Re-assessments: timetables for adoption

Brineura - cerliponase alfa - EMA/H/C/004065/S/0018, Orphan

BioMarin International Limited, Rapporteur:
Martina Weise, PRAC Rapporteur: Ulla Wändel
Liminga

IMVANEX - smallpox vaccine (live modified vaccinia virus ankara) - EMA/H/C/002596/S/0041

Bavarian Nordic A/S, Rapporteur: Jan
Mueller-Berghaus, PRAC Rapporteur: Brigitte
Keller-Stanislawski

Lojuxta - lomitapide - EMA/H/C/002578/S/0036

Amryt Pharmaceuticals DAC, Rapporteur: Johann
Lodewijk Hillege, PRAC Rapporteur: Menno van
der Elst

Mepsevii - vestronidase alfa - EMA/H/C/004438/S/0007, Orphan

Ultragenyx Germany GmbH, Rapporteur: Johann
Lodewijk Hillege, PRAC Rapporteur: Eva A.
Segovia

Naglazyme - galsulfase - EMA/H/C/000640/S/0078

BioMarin International Limited, Rapporteur:
Fátima Ventura, PRAC Rapporteur: Ana Sofia
Diniz Martins

B.6.5. Renewals of Marketing Authorisations: timetables for adoption provided only if the validation has been completed

Caprelsa - vandetanib - EMA/H/C/002315/R/0041

Genzyme Europe BV, Rapporteur: Alexandre
Moreau, PRAC Rapporteur: Ghania Chamouni

CRYSVITA - burosumab - EMA/H/C/004275/R/0009, Orphan

Kyowa Kirin Holdings B.V., Rapporteur: Kristina Dunder, Co-Rapporteur: Jayne Crowe, PRAC
Rapporteur: Brigitte Keller-Stanislawski

Gardasil 9 - human papillomavirus vaccine
[types 6, 11, 16, 18, 31, 33, 45, 52, 58]
(recombinant, adsorbed) -
EMA/H/C/003852/R/0035

MSD Vaccins, Rapporteur: Kristina Dunder,
Co-Rapporteur: Jan Mueller-Berghaus, PRAC
Rapporteur: Jean-Michel Dogné

Holoclar - ex vivo expanded autologous
human corneal epithelial cells containing
stem cells - EMA/H/C/002450/R/0026,
Orphan, ATMP

Chiesi Farmaceutici S.p.A., Rapporteur: Egbert Flory, Co-Rapporteur: Paolo Gasparini, CHMP
Coordinator: Jan Mueller-Berghaus and Daniela Melchiorri, PRAC Rapporteur: Rhea Fitzgerald

Jinarc - tolvaptan -
EMA/H/C/002788/R/0027

Otsuka Pharmaceutical Netherlands B.V.,
Rapporteur: Daniela Melchiorri, Co-Rapporteur:
Romaldas Mačiulaitis, PRAC Rapporteur: Amelia Cupelli

Prolia - denosumab -
EMA/H/C/001120/R/0082

Amgen Europe B.V., Rapporteur: Kristina Dunder, Co-Rapporteur: Jan Mueller-Berghaus,
PRAC Rapporteur: Ulla Wändel Liminga

Synjardy - empagliflozin / metformin -
EMA/H/C/003770/R/0044

Boehringer Ingelheim International GmbH,
Rapporteur: Johann Lodewijk Hillege,
Co-Rapporteur: Daniela Melchiorri, PRAC
Rapporteur: Eva A. Segovia

B.6.6. VARIATIONS – START OF THE PROCEDURE

Timetables for adoption provided that the validation has been completed.

B.6.7. Type II Variations scope of the Variations: Extension of indication

BLINCYTO - blinatumomab -
EMA/H/C/003731/II/0030, Orphan

Amgen Europe B.V., Rapporteur: Alexandre Moreau, Co-Rapporteur: Daniela Melchiorri,
PRAC Rapporteur: Eva Jirsová, "To modify the approved therapeutic indication to include the

treatment of Philadelphia chromosome positive CD19 positive B-cell precursor acute lymphoblastic leukaemia (ALL) in adult and paediatric patients with relapsed or refractory ALL and adult patients in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the PL are updated accordingly. The updated RMP version 10.0 has also been submitted."

Brilique - ticagrelor -

EMA/H/C/001241/II/0047/G

AstraZeneca AB, Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Maria Concepcion Prieto Yerro, PRAC Rapporteur: Menno van der Elst, "Extension of indication to include, in co administration with acetylsalicylic acid (ASA), the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) without a history of myocardial infarction who have undergone percutaneous coronary intervention (PCI) based on the final results of study D513BC00001 (THEMIS), a phase III multinational, randomised, double-blind, placebo controlled study to evaluate the effect of ticagrelor twice daily on the incidence of cardiovascular death, myocardial infarction or stroke in patients with T2DM; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated.

Update of section 4.8 of the SmPC with new safety information on traumatic haemorrhages based on the final results from study D513BC00001 (THEMIS) and data from the ticagrelor clinical development programme and post-marketing data.

The Package Leaflet is updated in accordance.

The RMP version 12 has also been submitted."

Invokana - canagliflozin -

EMA/H/C/002649/II/0046

Janssen-Cilag International NV, Rapporteur: Martina Weise, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Martin Huber, "Update of sections 4.1, 4.2, 4.8 and 5.1 of the Summary of Product Characteristics to add a new therapeutic indication for Invokana (canagliflozin) for the treatment of stage 2 or 3 chronic kidney disease and albuminuria, as an adjunct to standard of

care, in adults with type 2 diabetes mellitus. The proposed new indication is based upon new clinical efficacy and safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001).

The Package Leaflet is updated in accordance.

The RMP version 8.1 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet."

Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Ultomiris - ravulizumab -

EMEA/H/C/004954/II/0002, Orphan

Alexion Europe SAS, Rapporteur: Jorge Camarero Jiménez, Co-Rapporteur: Agnes Gyurasics, PRAC Rapporteur: Kimmo Jaakkola, "Extension of indication to include the treatment of patients with atypical hemolytic uremic syndrome (aHUS) for Ultomiris; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II.D is proposed to be updated to include the risk of thrombotic microangiopathy (TMA) with the new indication in the educational materials. The RMP version 1.6 has also been submitted."

Vokanamet - canagliflozin / metformin -

EMEA/H/C/002656/II/0051

Janssen-Cilag International NV, Rapporteur: Martina Weise, PRAC Rapporteur: Menno van der Elst, "Update of sections 4.1, 4.2, 4.8 and 5.1 of the Summary of Product Characteristics to add a new therapeutic indication for Vokanamet (canagliflozin/metformin) for the treatment of stage 2 or 3 chronic kidney disease and albuminuria, as an adjunct to standard of care, in adults with type 2 diabetes mellitus. The proposed new indication is based upon new clinical efficacy and safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001).

The Package Leaflet is updated in accordance.

The RMP version 8.1 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of

local representatives in the Package Leaflet.”
Request for 1 year of market protection for a new
indication (Article 14(11) of Regulation (EC)
726/2004)

B.6.8. CHMP assessed procedures scope: Pharmaceutical aspects

AMGEVITA - adalimumab -

EMA/H/C/004212/II/0019/G

Amgen Europe B.V., Rapporteur: Kristina Dunder

Bexsero - meningococcal group B vaccine (recombinant, component, adsorbed) -

EMA/H/C/002333/II/0079/G

GSK Vaccines S.r.l., Rapporteur: Kristina Dunder

Cresemba - isavuconazole -

EMA/H/C/002734/II/0024/G, Orphan

Basilea Pharmaceutica Deutschland GmbH,
Rapporteur: Johann Lodewijk Hillege

Empliciti - elotuzumab -

EMA/H/C/003967/II/0019/G

Bristol-Myers Squibb Pharma EEIG, Rapporteur:
Paula Boudewina van Hennik

Empliciti - elotuzumab -

EMA/H/C/003967/II/0020/G

Bristol-Myers Squibb Pharma EEIG, Rapporteur:
Paula Boudewina van Hennik

GONAL-f - follitropin alfa -

EMA/H/C/000071/II/0145/G

Merck Europe B.V., Rapporteur: Johann Lodewijk
Hillege

Kevzara - sarilumab -

EMA/H/C/004254/II/0015/G

sanofi-aventis groupe, Rapporteur: Jan
Mueller-Berghaus

LIBTAYO - cemiplimab -

EMA/H/C/004844/II/0002/G

Regeneron Ireland U.C., Rapporteur: Sinan B.
Sarac

Privigen - human normal immunoglobulin -

EMA/H/C/000831/II/0154/G

CSL Behring GmbH, Rapporteur: Jan
Mueller-Berghaus

Simulect - basiliximab -

EMA/H/C/000207/II/0101/G

Novartis Europharm Limited, Rapporteur: Jan

Mueller-Berghaus

Viramune - nevirapine -

EMA/H/C/000183/II/0141/G

Boehringer Ingelheim International GmbH,
Rapporteur: Bruno Sepodes

B.6.9. CHMP assessed procedures scope: Non-Clinical and Clinical aspects

Afstyla - lonococog alfa -

EMA/H/C/004075/II/0024

CSL Behring GmbH, Rapporteur: Jan
Mueller-Berghaus, "Update of sections 4.4 and
4.8 of the SmPC with safety information
regarding the development of factor VIII
inhibitors in patients treated with Afstyla based
on clinical trial and post-marketing data reviewed
recently with data lock point 03 January 2019.
The PL is updated accordingly. Additionally, local
representatives' details for Bulgaria and Croatia
have been updated."

Baraclude - entecavir -

EMA/H/C/000623/II/0063

Bristol-Myers Squibb Pharma EEIG, Rapporteur:
Filip Josephson, "Submission of responses to the
final clinical study report (CSR) from a Paediatric
Safety and Efficacy Study (AI463189), a
comparative study of the antiviral efficacy and
safety of Entecavir (ETV) versus placebo in
paediatric subjects with chronic Hepatitis B Virus
(HBV) infection who are HBeAg positive, in order
to provide additional clarification regarding the
on-treatment and long-term follow-up
haematology findings. The final CSR for
AI463189 was already submitted and assessed
within the context of procedure
EMA/H/C/000623/P46/010."

Empliciti - elotuzumab -

EMA/H/C/003967/II/0018

Bristol-Myers Squibb Pharma EEIG, Rapporteur:
Paula Boudewina van Hennik, "Update of section
5.1 of the SmPC with final overall survival data
from study CA204004 (A Phase 3, Randomized,
Open Label Trial of lenalidomide/dexamethasone
With or Without Elotuzumab in Relapsed or
Refractory Multiple Myeloma)."

EVOTAZ - atazanavir / cobicistat -

EMA/H/C/003904/II/0030

Bristol-Myers Squibb Pharma EEIG, Rapporteur:

Bruno Sepodes, "Update of sections 4.3 and 4.5 of the SmPC in order to add as contraindications the concomitant administration of dabigatran or lomitapide with Evotaz, and to add drug-drug interaction recommendations between Evotaz with direct oral anticoagulants and lomitapide (lipid modifying agent), based on already updated information in other marketing authorisations. Section 4.6 of the SmPC is also updated to reflect the accumulated information on the use of cobicistat during pregnancy, based on published literature. The package leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet."

Glivec - imatinib -

EMA/H/C/000406/II/0117

Novartis Europharm Limited, Rapporteur: Jorge Camarero Jiménez, "Update of section 4.6 of the SmPC to include that women of childbearing potential must be advised to use effective contraception for at least 15 days after stopping treatment with imatinib, based on a company review of the company Core Data Sheet. The PL has been updated accordingly."

Herzuma - trastuzumab -

EMA/H/C/002575/II/0023

Celltrion Healthcare Hungary Kft., Rapporteur: Jan Mueller-Berghaus, "C.I.13: Submission of the final report from study CT-P6 3.2. This is a phase 3, double blind, randomized, parallel-group, active-controlled study to compare the efficacy and safety of CT-P6 and Herceptin as Neoadjuvant and Adjuvant treatment in patients with HER2 positive early breast cancer."

Hizentra - human normal immunoglobulin -

EMA/H/C/002127/II/0110/G

CSL Behring GmbH, Rapporteur: Jan Mueller-Berghaus, "Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to include the number of PID patients, to include prescriber information and tolerability information for manual push infusion, to update prescriber information on device-assisted infusion and to include safety information, based on final results from study IgPro20_4004, an open-label study to evaluate the safety and tolerability of higher

infusion parameters of Hizentra infused manually or with pump assistance in PID patients.

Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update the number of PID patients and to include safety information based on final results from study IgPro_4005, a phase 4, open-label, single-sequence, crossover study to investigate the tolerability, safety and efficacy of biweekly Hizentra dosing in PID patients.

The Package Leaflet is updated accordingly.

In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representative in the Package Leaflet, to make some editorial updates in sections 4.2, 5.1 and 5.2 of the SmPC and to bring the PI in line with the latest QRD template version 10.1."

Imbruvica - ibrutinib -

EMA/H/C/003791/II/0053, Orphan

Janssen-Cilag International NV, Rapporteur: Filip Josephson, "The submission of final report on PFS by investigator assessment in Study PCYC-1112-CA, including PFS2 and overall survival data until study closure per protocol (ANX_003)"

Instanyl - fentanyl -

EMA/H/C/000959/II/0051

Takeda Pharma A/S, Rapporteur: Alexandre Moreau, "Update of section 4.8 to include dyspnoea. The MAH has also taken the opportunity to include editorial changes in Patient Leaflet."

Invanz - ertapenem -

EMA/H/C/000389/II/0060

Merck Sharp & Dohme B.V., Rapporteur: Bruno Sepodes, "To update sections 4.8 and 5.1 of the SmPC to update the safety information with the addition of a new post-marketing adverse reaction term: acute generalized exanthematous pustulosis (AGEP) and to update the breakpoints table with the most recent EUCAST recommendation (v 9.0, Jan 2019) on clinical breakpoints for ertapenem. Section 4 of the Package Leaflet is updated accordingly. The MAH is also updating the labeling section and the rest of the Product Information according to the latest QRD requirements and is updating List of Local Representatives."

Mepsevii - vestronidase alfa -**EMA/H/C/004438/II/0008, Orphan**

Ultragenyx Germany GmbH, Rapporteur: Johann Lodewijk Hillege, "Update of section 5.3 of the SmPC based on the final results from study UX003-PC010 a Developmental and Perinatal/Postnatal reproduction non-clinical study in rats including a Post-natal Behavioural/Functional Evaluation. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1."

Mylotarg - gemtuzumab ozogamicin -**EMA/H/C/004204/II/0010/G, Orphan**

Pfizer Europe MA EEIG, Rapporteur: Sinan B. Sarac, "A group of two type II variations, to submit the non-clinical in vitro study reports PFZ-07 and 6000572 relating to the effects of gemtuzumab ozogamicin on platelet development as well as on human platelet function."

PREVYMIS - letermovir -**EMA/H/C/004536/II/0013, Orphan**

Merck Sharp & Dohme B.V., Rapporteur: Filip Josephson, "Update of section 5.1 of the SmPC in order to update the viral resistance profile that may be associated with a change in susceptibility to letermovir considering new intro pharmacology data based on the analysis of the patients' samples included in the study MK-8228. This study is a Phase III Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV Seropositive Allogeneic Hematopoietic Stem Cell. This variation follows the recommendation dated 9th November 2017 that asked for the submission when available of the results to update the CMV phenotypic resistance analyses of all clinical isolates for subjects failing letermovir treatment and to explore the possibility to obtain additional pre-failure CMV genotypic data from available samples."

Xarelto - rivaroxaban -**EMA/H/C/000944/II/0068**

Bayer AG, Rapporteur: Kristina Dunder, "Update of section 5.1 of the SmPC based on results from

the pantoprazole/placebo randomization part of the COMPASS study; this is part of a double-blind, double-dummy randomized trial in which pantoprazole is being compared with placebo in patients participating in the trial who are not receiving a proton-pump inhibitor. In addition, an amendment to the COMPASS Clinical Study Report is submitted to correct values caused by a programming error in the statistical outputs in this study. No changes on the approved label are proposed due to this correction.”

**Zytiga - abiraterone acetate -
EMA/H/C/002321/II/0058**

Janssen-Cilag International NV, Rapporteur:
Jorge Camarero Jiménez, “To update section 5.1 of the SmPC based on final results from study PCR3011 (Latitude); this is a randomized, double-blind, placebo-controlled study designed to determine the efficacy of abiraterone acetate and low-dose prednisone in men with metastatic hormone-naive prostate cancer.”

**Zytiga - abiraterone acetate -
EMA/H/C/002321/II/0059**

Janssen-Cilag International NV, Rapporteur:
Jorge Camarero Jiménez, “To update sections 4.4 and 4.8 of the SmPC with safety information on QT prolongation and Torsades de Pointes following a cumulative review of QT Prolongation/Torsades de pointes occurrence.”

WS1636/G

**Mekinist-EMA/H/C/002643/WS1636/
0035/G**

**Tafinlar-EMA/H/C/002604/WS1636/
0040/G**

Novartis Europharm Limited, Lead Rapporteur:
Filip Josephson, “Update of section 5.1 of the Mekinist (trametinib) and Tafinlar (dabrafenib) SmPC to include the 5-years overall survival (OS) results from study MEK115306 (COMBI-d), a phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable or metastatic BRAF V600/K mutation-positive cutaneous melanoma and the 5-years overall survival (OS) results from study MEK116513 (COMBI-v), a phase III, open-label, 2 arm,

randomised study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma.”

WS1683

Elebrato Ellipta-EMEA/H/C/004781/

WS1683/0012

Temybric Ellipta-EMEA/H/C/005254/

WS1683/0001

Trelegy Ellipta-EMEA/H/C/004363/

WS1683/0010

GlaxoSmithKline Trading Services Limited, Lead Rapporteur: Peter Kiely, “Update of SmPC in order to add information in section 5.1 on survival data from the IMPACT study”

B.6.10. CHMP-PRAC assessed procedures

Eliquis - apixaban -

EMEA/H/C/002148/II/0063

Bristol-Myers Squibb / Pfizer EEIG, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Menno van der Elst, “Update of sections 4.4 and 4.9, of the SmPC in order to reflect the availability of a reversal agent for apixaban following the recent approval of andexanet alfa in the EU; the Package Leaflet and Labelling are updated accordingly. The RMP version 20 has also been submitted, with updates due to the availability of a reversal agent and implement the revised GVP template Rev.2. As a result, the list of safety concerns has been updated and a number of safety concerns listed as missing information have been reclassified and have been removed from the RMP.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to update the information in the SmPC and Package Leaflet in accordance with the most recent guidance on labelling of excipients of medicinal products for human use.”

Gardasil 9 - human papillomavirus vaccine

[types 6, 11, 16, 18, 31, 33, 45, 52, 58]

(recombinant, adsorbed) -

EMEA/H/C/003852/II/0033

MSD Vaccins, Rapporteur: Kristina Dunder, PRAC Rapporteur: Jean-Michel Dogné, “Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in

order to update the safety and immunogenicity information based on final results from study V503-P004 listed as a category 3 study in the RMP (MEA007); this is an open-label phase III clinical trial to study the immunogenicity and tolerability of Gardasil 9 in adult women (27 to 45 year-olds) compared to young adult women (16 to 26 year-olds); the Package Leaflet is updated accordingly. The RMP version 4.1 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC according to the Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017), and to include editorial changes in Section 5.1 of the SmPC"

Imbruvica - ibrutinib -

EMA/H/C/003791/II/0052, Orphan

Janssen-Cilag International NV, Rapporteur: Filip Josephson, PRAC Rapporteur: Nikica Mirošević Skvrce, "submission of the final report on the long term safety study PAM 3038-1, which assessed long term safety data collected from predefined cohorts of subjects treated with ibrutinib for up to 5 years or until disease progression or unacceptable toxicity at the recommended daily doses of 420 mg/day for CLL/SLL and 560 mg/day for MCL. This final report fulfils the milestone for the Post Approval Measure MEA025"

Keytruda - pembrolizumab -

EMA/H/C/003820/II/0080

Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Menno van der Elst, "To update sections 4.2, 4.4 and 4.8 of the SmPC on the safety information for immune-related endocrinopathies following a safety review for Addison's disease/Primary adrenal insufficiency. The updated RMP version 26.1 has also been submitted. The MAH also took the opportunity to include the changes in Annex II related to the new EMA QRD template version 10.1 and to update the List of Local Representatives of Portugal in the Package Leaflet."

Myozyme - alglucosidase alfa -

EMA/H/C/000636/II/0075

Genzyme Europe BV, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Adrien Inoubli,

“Update of sections 4.4 and 5.1 of the Summary of Product Characteristics in order to reflect changes in the existing warning on immunogenicity and immunomodulation and add new clinical information on infantile onset patients (IOPD) immune tolerance induction based on data on use of immune tolerance induction in infantile onset Pompe disease patients from two exploratory Phase 4 studies (AGLU03707 / MSC12817 and companion study AGLU03807/ MSC12892) and the Duke Center of Excellence Observational Study (01562). The updated RMP version 9.0 has also been submitted.”

Raxone - idebenone -

EMA/H/C/003834/II/0016, Orphan

Santhera Pharmaceuticals (Deutschland) GmbH, Rapporteur: John Joseph Borg, PRAC Rapporteur: Amelia Cupelli, “C.I.11 for SOB studies: Submission of the final report from study SNT-CRS-002 listed as a Specific Obligation (SOB10, former SOB2) in the Annex II of the Product Information. This is a Historical case record survey (CRS) of visual acuity data from patients with Leber’s hereditary optic neuropathy (LHON). The goal is to generate a natural history group to serve as a comparator group of idebenone-naïve patients for the open-label study SNT-IV-005 which will assess long-term efficacy and safety in patients with LHON treated with Raxone. Annex II is modified accordingly. Submission of an updated RMP version 1.8 accordingly.”

RoActemra - tocilizumab -

EMA/H/C/000955/II/0086/G

Roche Registration GmbH, Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Brigitte Keller-Stanislawski, “Grouping of 3 variations: 2 variations C.I.11.z supporting RMP updates: Submission of an updated RMP version 25.2 in order to remove the reference to the Neutropenia Guided Questionnaire as per the Guidance on the format of the RMP in EU EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2 and to remove all references to the US Claims Database from the RMP resulting from the conversion of the RMP to the new template. The MAH also took the opportunity to make the following minor changes to the RMP:

- Removal of study WA22479 (British Society of Rheumatology Biologics Register (BSRBR)) in response to the fulfilment of PAM MEA-045.
- Removal of OTIS registry from additional pharmacovigilance activities which was erroneously retained in EU- RMP version 24.1 approved with the variation procedure EMEA/H/C/00955/II/76.
- Inclusion of the ZUMA-8 (KTE-X19-108) study in routine pharmacovigilance activities in line with previous PRAC/CHMP request as part of variation procedure EMEA/H/C/000955/II/0076.
- Removal of study WA29358 which was erroneously introduced into RMP v24.1 as an additional PV activity

1 variation C.I.4 affecting the PI

Update of sections 4.8 of the SmPC the change the frequency for anaphylaxis (fatal) and Stevens-Johnson Syndrome to "rare" in the SmPC; the Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to Sections 4.2, 4.8 and 5.1 of the SmPC, the Annex IID and Section 4 of the Package Leaflet."

**Tamiflu - oseltamivir -
EMEA/H/C/000402/II/0142**

Roche Registration GmbH, Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Kirsti Villikka, "Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following completion of the paediatric studies NV25719 and NV20234 and downstream population PK and PK/PD analysis, listed in the approved Tamiflu Paediatric Investigation Plan (PIP) (EMEA-000365-PIP01-08-M10); the study NV25719 was a prospective, open-label, randomized study which investigated PK and PD of two weight adjusted oseltamivir doses for the treatment of influenza-infected immunocompromised (IC) children less than 13 years of age. The study NV20234 was a prospective, double-blind, randomized trial which investigated safety and viral resistance to oseltamivir treatment in influenza-infected IC adults, adolescents and children. The purpose of this variation is to establish a dose recommendation for the treatment of paediatric IC patients.

The Package Leaflet and Labelling are updated accordingly.

The updated RMP version 19 has also been submitted.”

VeraSeal - human fibrinogen / human thrombin - EMEA/H/C/004446/II/0006/G

Instituto Grifols, S.A., Rapporteur: Andrea Laslop, PRAC Rapporteur: Amelia Cupelli, “B.IV.1.a.3 – Type II - To add a new CE marked applicator tip as a replacement for the current application cannula which allows the application of the product both by dripping and spraying without gas assistance. The safety concern of air or gas embolism that is currently included in the Risk Management Plan (RMP) is no longer applicable, consequently the RMP has been updated accordingly (version 4.0) and is provided in Module 1.8.2. RMP version 4.0 has been restructured in order to adapt to the new format of GVP Module V.

B.II.e.6.a – Type 1B

B.II.e.6.a – Type 1B

B.II.b.3.a – Type 1A

B.II.b.3.a – Type 1A

B.6.11. PRAC assessed procedures

PRAC Led

Accofil - filgrastim - EMEA/H/C/003956/II/0037

Accord Healthcare S.L.U., Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Kirsti Villikka, PRAC-CHMP liaison: Tuomo Lapveteläinen, “Submission of an updated RMP version 4.0 in order to update the section of additional pharmacovigilance activities (removal of SCNIR and EBMT registry) following the conclusion of `Accofil Severe Chronic Neutropenia International Registry (SCNIR) and European Group for Blood and Marrow Transplantation (EBMT) Combined Analysis Report. The MAH has taken the occasion also to implement the RMP template based on GVP revision 2 guideline.”

PRAC Led

Caprelsa - vandetanib - EMEA/H/C/002315/II/0040

Genzyme Europe BV, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni, PRAC-CHMP liaison: Alexandre Moreau,

“Submission of an updated RMP version 13 in order to remove the Health Care Professionals survey from the list of additional Pharmacovigilance Activities and to remove several safety concerns from the list of important identified and potential risks and missing information to follow revised guidance in the GVP Module V Rev.2 as requested during variation procedure no. EMEA/H/C/002315/II/0028.”

PRAC Led

Edurant - rilpivirine -

EMEA/H/C/002264/II/0037

Janssen-Cilag International NV, PRAC

Rapporteur: Menno van der Elst, PRAC-CHMP

liaison: Johann Lodewijk Hillege, “C.I.13:

Submission of the final report from a Drug Utilization Study (DUS), with register number EUPAS5766, in the EuroSIDA cohort listed as a category 3 study in the RMP.

This is an Observational Cohort Study to assess rilpivirine (RPV) utilization according to the European SmPC.

The RMP version 9.0 has also been submitted.”

PRAC Led

EXJADE - deferasirox -

EMEA/H/C/000670/II/0068

Novartis Europharm Limited, Rapporteur:

Alexandre Moreau, PRAC Rapporteur: Ghania

Chamouni, PRAC-CHMP liaison: Alexandre

Moreau, “Submission of the final report related to the Physician Survey (NO6987) conducted for Exjade to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and to assess the awareness and appropriate use of both formulations (Dispersible Tablets and Film-Coated tablets). The updated RMP version 17.1 is submitted as well.”

PRAC Led

Glivec - imatinib -

EMEA/H/C/000406/II/0115

Novartis Europharm Limited, Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Eva A.

Segovia, PRAC-CHMP liaison: Maria Concepcion

Prieto Yerro, “Submission of an updated RMP version 12 in order to revise the lists of safety concerns in EU RMP and align with the current GVP Rev 2 based on the PRAC advice received on

the latest PSUR (11-May-2015 to 10-May-2018)."

PRAC Led

**Jakavi - ruxolitinib -
EMA/H/C/002464/II/0043**

Novartis Europharm Limited, Rapporteur: Filip Josephson, PRAC Rapporteur: Annika Folin, PRAC-CHMP liaison: Filip Josephson, "Submission of the final report from a safety study (INC424AIC01T) of ruxolitinib in myelofibrosis (MF) listed as a category 3 study in the RMP. This is a non-interventional, observational post-authorisation safety study (PASS) intended to provide real-world safety data on patients with MF who were exposed and non-exposed to ruxolitinib and thereby provide insights into disease management and the safety profile of ruxolitinib.

The RMP version 11 has also been submitted. The updated RMP v11 reflects the completion of additional pharmacovigilance studies including the above-mentioned PASS (INC424AIC01T, Category 3) as well as the RESPONSE study (INC424B2301, Category 1). This RMP is incorporated in this variation and will be cross-referred in the variation forthcoming submission for the RESPONSE study within a month of this submission."

PRAC Led

**Onivyde - irinotecan hydrochloride
trihydrate - EMA/H/C/004125/II/0015,
Orphan**

Les Laboratoires Servier, PRAC Rapporteur: David Olsen, PRAC-CHMP liaison: Ingrid Wang, "Submission of an updated RMP version 2.7 in order to update the RMP further to the last PSUSA procedures (PSUSA/00010534/201804 and (PSUSA/00010534/201810) and in accordance with GVP Module V Rev.2."

PRAC Led

**WS1614
Enbrel-EMA/H/C/000262/WS1614/0227
LIFMIOR-EMA/H/C/004167/WS1614/
0021**

Pfizer Europe MA EEIG, Lead Rapporteur: Maria Concepcion Prieto Yerro, Lead PRAC Rapporteur: Eva A. Segovia, PRAC-CHMP liaison: Maria Concepcion Prieto Yerro, "Submission of the final

report from study (B1801035; PURPOSE) listed as a category 3 study in the RMP. This is a non-interventional, multi-centre, prospective, observational, cohort study conducted to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to paediatric patients for the treatment of plaque psoriasis.”

PRAC Led

WS1651

Idacio-EMEA/H/C/004475/WS1651/0003

Kromeya-EMEA/H/C/005158/WS1651/0003

Fresenius Kabi Deutschland GmbH, Lead PRAC
Rapporteur: Ulla Wändel Liminga, PRAC-CHMP
liaison: Kristina Dunder, “To update the risk management plans (RMP) for Idacio and Kromeya in order to align it with the parent product Humira one.

The Risk Minimization Measures in Annex II.D of the PI are also updated.

Minor linguistic changes/corrections to the Product Information in German, French, Hungarian (Idacio only) and Slovenian have been included.”

PRAC Led

WS1663/G

Exviera-EMEA/H/C/003837/WS1663/

0046/G

Viekirax-EMEA/H/C/003839/WS1663/

0055/G

AbbVie Deutschland GmbH & Co. KG, Lead
Rapporteur: Filip Josephson, Lead PRAC
Rapporteur: Maria del Pilar Rayon, PRAC-CHMP
liaison: Maria Concepcion Prieto Yerro, “C.I.13
To submit the final report from study P15-421, listed as a category 3 study in the RMP. This was a prospective, observational cohort study utilizing the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for Hepatitis C with paritaprevir with ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-DAA regimen) or paritaprevir/r and ombitasvir (2-DAA regimen) with or without ribavirin for Hepatitis C Infection (HCV)

C.I.11.Z (Type IB): To change the final due date

for the prospective safety study report in order to evaluate the recurrence of hepatocellular carcinoma associated with Viekirax and Exviera from Q2 2021 to Q2 2023. Annex II of the Product Information is updated accordingly.
An updated RMP version 5.0 has also been submitted.”

PRAC Led

WS1671

Afinitor-EMEA/H/C/001038/WS1671/0063

Votubia-EMEA/H/C/002311/WS1671/0059

Novartis Europharm Limited, Lead Rapporteur: Janet Koenig, Lead PRAC Rapporteur: Martin Huber, PRAC-CHMP liaison: Janet Koenig, “To update the RMP for Afinitor and Votubia to version 14.0 to change the safety concerns, to reflect the completion of pharmacovigilance studies [CRAD001Y2201 (Afinitor II/0058), CRAD001M2304 (Votubia II/0051), CRAD001J2301 (Afinitor II/0051G), CRAD00W2301 (Afinitor II/0051G)] and to implement the latest GVP module V rev.2 template. The change has been agreed by the PRAC in the outcome of a PSUR assessment (EMEA/H/C/PSUSA/00010268/201703).”

PRAC Led

WS1680

Actos-EMEA/H/C/000285/WS1680/0082

Competact-EMEA/H/C/000655/WS1680/0074

Glubrava-EMEA/H/C/000893/WS1680/0060

Glustin-EMEA/H/C/000286/WS1680/0081

Tandemact-EMEA/H/C/000680/WS1680/0060

Takeda Pharma A/S, Lead Rapporteur: Peter Kiely, Lead PRAC Rapporteur: Rhea Fitzgerald, PRAC-CHMP liaison: Jayne Crowe, “Submission of an updated RMP (version 27) in order to update and consolidate within a single RMP the RMPs for Pioglitazone, Pioglitazone/Metformin fixed dose combination (FDC) and Pioglitazone/Glimepiride FDC. The list of safety concerns has also been reviewed and consolidated RMP version updated with information agreed/approved as part of the PSUR procedure (EMEA/H/C/PSUSA/00002417/201807) with

regards to discontinuation of pioglitazone aRMMs.”

B.6.12. CHMP-CAT assessed procedures

B.6.13. CHMP-PRAC-CAT assessed procedures

Strimvelis - autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence - EMEA/H/C/003854/II/0022, Orphan, ATMP

Orchard Therapeutics (Netherlands) BV,
Rapporteur: Sol Ruiz, CHMP Coordinator: Maria Concepcion Prieto Yerro, PRAC Rapporteur: Menno van der Elst, “Submission of an updated RMP version 2.0 in order to introduce changes to the design of the post-authorisation study STRIM-002, from a prospective to a retrospective study.

Following additional minor changes to the RMP are also included: Update of the RMP in line with EMA Rev.2.0.1 template; update of the RMP to make the necessary amendments to the name of the MAH following the MAH transfer; update of the data in the RMP in line with the updated data lock point; update of timelines for the STRIM-001 study.”

B.6.14. PRAC assessed ATMP procedures

B.6.15. Unclassified procedures and worksharing procedures of type I variations

WS1676/G

Exelon-EMEA/H/C/000169/WS1676/0124/G

Prometax-EMEA/H/C/000255/WS1676/0125/G

Novartis Europharm Limited, Lead Rapporteur: Alexandre Moreau

WS1681

Esperoct-EMEA/H/C/004883/WS1681/0001

NovoEight-EMEA/H/C/002719/WS1681/0032

Novo Nordisk A/S, Lead Rapporteur: Jan Mueller-Berghaus

WS1687

Fiasp-EMEA/H/C/004046/WS1687/0017
NovoMix-EMEA/H/C/000308/WS1687/0100
NovoRapid-EMEA/H/C/000258/WS1687/0130
Ryzodeg-EMEA/H/C/002499/WS1687/0037

Novo Nordisk A/S, Lead Rapporteur: Kristina Dunder

B.7. DOCUMENTS TABLED IN MMD AFTER THE CHMP PLENARY

B.7.1. Yearly Line listing for Type I and II variations

B.7.2. Monthly Line listing for Type I variations

B.7.3. Opinion on Marketing Authorisation transfer (MMD only)

B.7.4. Notifications in accordance with Article 61(3) of Council Directive 2001/83/EC (MMD only)

B.7.5. Request for supplementary information relating to Notification of Type I variation (MMD only)

B.7.6. Notifications of Type I Variations (MMD only)

C. Annex C - Post-Authorisation Measures (PAMs), (Line listing of Post authorisation measures with a description of the PAM. Procedures starting in that given month with assessment timetabled)

D. Annex D - Post-Authorisation Measures (PAMs), (Details on PAMs including description and conclusion, for adoption by CHMP in that given month, or finalised ones with PRAC recommendation and no adoption by CHMP needed)

E. Annex E - EMEA CERTIFICATION OF PLASMA MASTER FILES

Information related to plasma master files cannot be released at the present time as these contain commercially confidential information.

F. ANNEX F - Decision of the Granting of a Fee Reduction/Fee Waiver

F.1. Parallel Distribution - Pursuant to Article 9 of Council Regulation (EC) No. 2743/98 of 14 December 1998, as amended

F.2. Request for scientific opinion on justification of exceptional circumstance and for imperative grounds of public health

G. ANNEX G

H. ANNEX H - Product Shared Mailboxes – e-mail address

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the CHMP agenda and should be read in conjunction with the agenda or the minutes.

Oral explanations (section 2)

The items listed in this section are those for which marketing authorisation holders (MAHs) or applicants have been invited to the CHMP plenary meeting to address questions raised by the Committee. Oral explanations normally relate to on-going applications (section 3, 4 and 5) or referral procedures (section 10) but can relate to any other issue for which the CHMP would like to discuss with company representatives in person.

Initial applications (section 3)

This section lists applications for marketing authorisations of new medicines that are to be discussed by the Committee.

Section 3.1 is for medicinal products nearing the end of the evaluation and for which the CHMP is expected to adopt an **opinion** at this meeting on whether marketing authorisation should be granted. Once adopted, the CHMP opinion will be forwarded to the European Commission for a final legally binding decision valid throughout the EU.

The other items in the section are listed depending on the stage of the evaluation, which is shown graphically below:



The assessment of an application for a new medicine takes up to 210 'active' days. This active evaluation time is interrupted by at least one 'clock-stop' during which time the applicant prepares the answers to questions from the CHMP. The clock stop happens after day 120 and may also happen after day 180, when the CHMP has adopted a list of questions or outstanding issues to be addressed by the company. Related discussions are listed in the agenda under sections 3.2 (**Day 180 List of outstanding issues**) and 3.3 (**Day 120 list of questions**).

CHMP discussions may also occur at any other stage of the evaluation, and these are listed under section 3.4, **update on ongoing new applications for centralised procedures**.

The assessment leads to an opinion from the CHMP by day 210. Following a CHMP opinion the European Commission takes usually 67 days to issue a legally binding decision (i.e. by day 277 of the procedure). CHMP discussions on products that have received a CHMP opinion and are awaiting a decision are listed under section 3.6, **products in the decision making phase**.

Extension of marketing authorisations according to Annex I of Reg. 1234/2008 (section 4)

Extensions of marketing authorisations are applications for the change or addition of new strengths, formulations or routes of administration to existing marketing authorisations. Extension applications follow a 210-day evaluation process, similarly to applications for new medicines (see figure above).

Type II variations - Extension of indication procedures (section 5)

Type II variations are applications for a change to the marketing authorisation which requires an update of the product information and which is not covered in section 4. Type II variations include applications for a new use of the medicine (extension of indication), for which the assessment takes up to 90 days. For the applications listed in this section, the CHMP may adopt an opinion or request supplementary information from the applicant.

Ancillary medicinal substances in medical devices (section 6)

Although the EMA does not regulate medical devices it can be asked by the relevant authorities (the so-called Notified Bodies) that are responsible for regulating these devices to give a scientific opinion on a medicinal substance contained in a medical device.

Re-examination procedures (new applications) under article 9(2) of regulation no 726/2004 (section 3.5)

This section lists applications for new marketing authorisation for which the applicant has requested a re-examination of the opinion previously issued by the CHMP.

Re-examination procedures (section 5.3)

This section lists applications for type II variations (including extension of indication applications) for which the applicant has requested re-examination of the opinion previously issued by the CHMP.

Withdrawal of application (section 3.7)

Applicants may decide to withdraw applications at any stage during the assessment and a CHMP opinion will therefore not be issued. Withdrawals are included in the agenda for information or discussion, as necessary.

Procedure under article 83(1) of regulation (EC) 726/2004 (compassionate use) (section 7)

Compassionate use is a way of making available to patients with an unmet medical need a promising medicine which has not yet been authorised (licensed) for their condition. Upon request, the CHMP provides recommendations to all EU Member States on how to administer, distribute and use certain medicines for compassionate use.

Pre-submission issues (section 8)

In some cases the CHMP may discuss a medicine before a formal application for marketing authorisation is submitted. These cases generally refer to requests for an accelerated assessment for medicines that are of major interest for public health or can be considered a therapeutic innovation. In case of an accelerated assessment the assessment timetable is reduced from 210 to 150 days.

Post-authorisation issues (section 9)

This section lists other issues concerning authorised medicines that are not covered elsewhere in the agenda. Issues include supply shortages, quality defects, some annual reassessments or renewals or type II variations to marketing authorisations that would require specific discussion at the plenary.

Referral procedures (section 10)

This section lists referrals that are ongoing or due to be started at the plenary meeting. 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 EU. Further information on such procedures can be found [here](#).

Pharmacovigilance issues *(section 11)*

This section lists issues that have been discussed at the previous meeting of the PRAC, the EMA's committee responsible for evaluating and monitoring safety issues for medicines. Feedback is provided by the PRAC. This section also refers to the early notification system, a system used to notify the European regulatory network on proposed EMA communication on safety of medicines.

Inspections Issues *(section 12)*

This section lists inspections that are undertaken for some medicinal products. Inspections are carried out by regulatory agencies to ensure that marketing authorisation holders comply with their obligations. Inspection can relate to good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP) or good pharmacovigilance practice (GVP).

Innovation task force *(section 13)*

The Innovation Task Force (ITF) is a body set up to encourage early dialogue with applicants developing innovative medicines. Minutes from the last ITF meeting as well as any related issue that requires discussion with the CHMP are listed in this section of the agenda. Further information on the ITF can be found [here](#).

Scientific advice working party (SAWP) *(section 14.3.1)*

This section refers to the monthly report from the CHMP's Scientific Advice Working Party (SAWP) on scientific advice given to companies during the development of medicines. Further general information on SAWP can be found [here](#).

Satellite groups / other committees *(section 14.2)*

This section refers to the reports from groups and committees making decisions relating to human medicines: the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), the Committee for Orphan Medicinal Products (COMP), the Committee for Herbal Medicinal Products (HMPC), Paediatric Committee (PDCO), the Committee for Advanced Therapies (CAT) and the Pharmacovigilance Risk Assessment Committee (PRAC).

Invented name issues *(section 14.3)*

This section list issues related to invented names proposed by applicants for new medicines. The CHMP has established the Name Review Group (NRG) to perform reviews of the invented names. The group's main role is to consider whether the proposed names could create a public-health concern or potential safety risk. Further information can be found [here](#).

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