25 March 2019
EMA/CHMP/190227/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for medicinal products for human use (CHMP)

Final agenda for the meeting on 25-28 March 2019

Chair: Harald Enzmann – Vice-Chair: Bruno Sepodes

25 March 2019, 13:00 – 19:30, room 1C – Amsterdam, The Netherlands

26 March 2019, 08:30 – 19:30, room 1C – Amsterdam, The Netherlands

27 March 2019, 08:30 – 19:30, room 1C – Amsterdam, The Netherlands

28 March 2019, 08:30 – 15:00, room 1C – Amsterdam, The Netherlands

Health and safety information

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

Disclaimers

Some of the information contained in this agenda 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. Additional details on some of these procedures will be published in the CHMP meeting highlights once the procedures are finalised and start of referrals will also be available.

Of note, this agenda is a working document primarily designed for CHMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda 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. Welcome and declarations of interest of members, alternates and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the CHMP plenary session to be held 25-28 March 2019. See (current) March 2019 CHMP minutes (to be published post April 2019 CHMP meeting).

1.2. Adoption of agenda

CHMP agenda for 25-28 March 2019

1.3. Adoption of the minutes

CHMP minutes for 25-28 February 2019.

ORGAM minutes for 18 March 2019.

2. Oral Explanations

2.1. Pre-authorisation procedure oral explanations

2.1.1. trientine dihydrochloride - Orphan - EMEA/H/C/004111

Univar BV; treatment of Wilson's disease

Scope: Oral explanation

Action: Oral explanation to be held on 26 March 2019 at time 14:00

List of Outstanding Issues adopted on 31.01.2019. List of Questions adopted on 28.06.2018.

2.1.2. hydroxycarbamide - EMEA/H/C/004837

prevention of complications of Sickle Cell disease

Scope: Oral explanation

Action: Oral explanation to be held on 27 March 2019 at time 09:00

List of Outstanding Issues adopted on 15.11.2018. List of Questions adopted on 28.06.2018.

2.1.3. cemiplimab - EMEA/H/C/004844

as monotherapy, indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma

Scope: Oral explanation

Action: Oral explanation to be held on 26 March 2019 at time 11:00

List of Outstanding Issues adopted on 31.01.2019. List of Questions adopted on 26.07.2018.

2.2. Re-examination procedure oral explanations

No items

2.3. Post-authorisation procedure oral explanations

2.3.1. Revlimid - lenalidomide - Orphan - EMEA/H/C/000717/II/0102/G

Celgene Europe BV

Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni

Scope: Oral explanation

Action: Oral explanation to be held on 26 March 2019 at time 09:00

Request for Supplementary Information adopted on 15.11.2018.

See 5.1

2.4. Referral procedure oral explanations

2.4.1. Omega-3-acid-ethyl esters- containing medicinal products for oral use – EMEA/H/A-31/1464

MAHs: various

Re-examination Rapporteur: John Joseph Borg, Re-examination Co-Rapporteur: Johann Lodewijk Hillege

Scope: Oral explanation on Re-examination, SAG Report

Action: Oral explanation to be held on 27 March 2019 at time 15:30

Review of the benefit-risk balance following notification by the MPA in Sweden on 15 March 2018 of a referral under Article 31 of Directive 2001/83/EC.

See 10.6

3. Initial applications

3.1. Initial applications; Opinions

3.1.1. autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - Orphan - ATMP - EMEA/H/C/003691

Accelerated assessment

bluebird bio GmbH; treatment of transfusion-dependent β-thalassaemia (TDT)

Scope: Opinion

Action: For adoption

List of Questions adopted on 25.01.2019.

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

3.2.1. turoctocog alfa pegol - Orphan - EMEA/H/C/004883

Novo Nordisk A/S; treatment and prophylaxis of bleeding in patients with haemophilia A

Scope: List of outstanding issues

Action: For adoption

List of Outstanding Issues adopted on 15.11.2018. List of Questions adopted on 26.07.2018.

3.2.2. angiotensin II - EMEA/H/C/004930

treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy

Scope: List of outstanding issues

Action: For adoption

List of Questions adopted on 18.10.2018.

3.2.3. ciprofloxacin - EMEA/H/C/004394

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

Scope: List of outstanding issues

Action: For adoption

List of Questions adopted on 26.07.2018.

3.2.4. L-lysine hydrochloride / L-arginine hydrochloride - EMEA/H/C/004541

reduction of renal radiation exposure during Peptide-Receptor Radionuclide Therapy (PRRT) with lutetium (^{177}Lu) oxodotreotide

Scope: List of outstanding issues

Action: For adoption

List of Questions adopted on 18.10.2018.

3.2.5. botulinum toxin type a - EMEA/H/C/004587

temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows

Scope: List of outstanding issues

Action: For adoption

List of Outstanding Issues adopted on 18.10.2018. List of Questions adopted on 09.11.2017.

3.2.6. posaconazole - EMEA/H/C/005028

treatment of fungal infections in adults

Scope: List of outstanding issues

Action: For adoption

List of Questions adopted on 18.10.2018.

3.2.7. larotrectinib - Orphan - EMEA/H/C/004919

Bayer AG; treatment of adult and paediatric patients with locally advanced or metastatic solid tumours

Scope: List of outstanding issues, List of experts for the SAG Oncology meeting adopted via written procedure on 16 March 2019

Action: For adoption

List of Questions adopted on 11.12.2018.

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

3.3.1. 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, treatment of juvenile idiopathic arthritis, paediatric plaque psoriasis, paediatric Crohn's disease, adolescent hidradenitis suppurativa, paediatric uveitis, treatment of juvenile idiopathic arthritis, paediatric plaque psoriasis, paediatric Crohn's disease, paediatric uveitis

Scope: List of questions

Action: For adoption

3.3.2. deferasirox - EMEA/H/C/005156

treatment of chronic iron overload

Scope: List of questions

Action: For adoption

3.3.3. imipenem / cilastatin / relebactam - EMEA/H/C/004808

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

Scope: List of questions

Action: For adoption

3.3.4. osilodrostat - Orphan - EMEA/H/C/004821

Novartis Europharm Limited; treatment of Cushing's syndrome

Scope: List of questions

Action: For adoption

3.3.5. solriamfetol - EMEA/H/C/004893

is indicated to improve wakefulness in patients with narcolepsy or obstructive sleep apnoea

Scope: List of questions

Action: For adoption

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

3.4.1. viable T-cells - Orphan - ATMP - EMEA/H/C/002397

Kiadis Pharma Netherlands B.V.; adjunctive treatment in haematopoietic stem cell transplantation (HSCT) for a malignant disease

Scope: Request by the applicant for an extension to the clock stop to respond to the List of Outstanding Issues adopted on 20.09.2018

Action: For adoption

List of Outstanding Issues adopted on 20.09.2018, 25.05.2018. List of Questions adopted on 08.09.2017.

3.4.2. cannabidiol - Orphan - EMEA/H/C/004675

GW Research Ltd; adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)

Scope: Letter from third party

Action: For discussion

List of Outstanding Issues adopted on 31.01.2019, 15.11.2018. List of Questions adopted on 31.05.2018.

3.4.3. romosozumab - EMEA/H/C/004465

treatment of osteoporosis

Scope: Letter from applicant dated 13 March 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted on 28.02.2019.

Action: For adoption

List of Outstanding Issues adopted on 28.02.2019, 15.11.2018, 20.09.2018. List of Questions adopted on 26.04.2018.

3.4.4. rituximab - EMEA/H/C/004696

treatment of Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL) and Rheumatoid arthritis

Scope: Amended list of questions, updated timetable

Action: For adoption

List of questions adopted on 13.12.2018.

3.4.5. crisaborole - EMEA/H/C/004863

treatment of mild to moderate atopic dermatitis

Scope: Letter from applicant dated 08 March 2019 requesting an extension of clock stop to respond to the list of outstanding issues adopted on 28.02.2019.

Action: For adoption

List of outstanding issues adopted on 28.02.2019. List of Questions adopted on 20.09.2018.

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

3.5.1. Doxolipad - doxorubicin hydrochloride - EMEA/H/C/004110

TLC Biopharmaceuticals B.V.; treatment of breast and ovarian cancer

Scope: Updated timetable

Action: For adoption

Hybrid application (Article 10(3) of Directive No 2001/83/EC)

Opinion adopted on 31.01.2019. List of Outstanding Issues adopted on 26.07.2018. List of Questions adopted on 14.09.2017.

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

4.1.1. Trisenox - arsenic trioxide - EMEA/H/C/000388/X/0068

Teva B.V.

Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni

Scope: “Extension application to add a new strength of 2 mg/ml. The RMP (version 2.0) is updated in accordance.”

Action: For adoption

List of Outstanding Issues adopted on 31.01.2019. List of Questions adopted on 20.09.2018.

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

4.3.1. Akynzeo - fosnetupitant / netupitant / palonosetron - EMEA/H/C/003728/X/0018

Helsinn Birex Pharmaceuticals Limited

Rapporteur: Peter Kiely, Co-Rapporteur: Alexandre Moreau, PRAC Rapporteur: Amelia Cupelli

Scope: "Extension application to introduce the new pharmaceutical form 'powder for concentrate for solution for infusion' and a new strength for the fixed combination of fosnetupitant (pro-drug of netupitant) and palonosetron of 235 mg/0.25 mg, to be administered intravenously (new route of administration)."

Action: For adoption

4.3.2. Carbaglu - carglumic acid - Orphan - EMEA/H/C/000461/X/0038

Orphan Europe SARL

Rapporteur: Fátima Ventura

Scope: "Extension application to introduce a new pharmaceutical form associated with 2 new strengths (200 mg and 800 mg soluble tablets)."

Action: For adoption

4.3.3. Imraldi - adalimumab - EMEA/H/C/004279/X/0019/G

Samsung Bioepis NL B.V.

Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Ulla Wändel Liminga

Scope: "Extension application to introduce a new presentation of 40 mg/0.8 ml solution for injection in a vial, to allow the administration to paediatric patients requiring less than a full 40mg dose.
C.I.z - To update the Product Information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application.
The RMP (version 3.0) is updated in accordance.
In addition, the applicant took the opportunity to implement minor editorial changes ."

Action: For adoption

4.3.4. Remsima - infliximab - EMEA/H/C/002576/X/0062

Celltrion Healthcare Hungary Kft.

Rapporteur: Outi Mäki-Ikola, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Kimmo Jaakkola

Scope: “Extension application to introduce a new pharmaceutical form (solution for injection), a new strength (120 mg) and a new route of administration (subcutaneous use).
The RMP (version 9.1) is updated in accordance.”

Action: For adoption

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

5.1.1. Axumin - fluciclovine (^{18}F) - EMEA/H/C/004197/II/0011

Blue Earth Diagnostics Ireland Limited

Rapporteur: Janet Koenig, PRAC Rapporteur: Rugile Pilviniene

Scope: “Extension of indication to include diagnosis and continuing assessment of Glioma in adult patients as a new indication for Axumin; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 and 11 of the SmPC and the Annex II are updated. The Package Leaflet is updated in accordance.” Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Action: For adoption

5.1.2. Cyramza - ramucirumab - EMEA/H/C/002829/II/0027

Eli Lilly Nederland B.V.

Rapporteur: Paula Boudewina van Hennik, Co-Rapporteur: Kolbeinn Gudmundsson (IS) (MNAT with FI for Quality, FI for Non-Clinical, LT for Clinical Pharmacology), PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: “Extension of indication to include Cyramza indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in accordance. The Package Leaflet is updated in accordance. RMP version 8.1 has been submitted.” Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Action: For adoption

Request for Supplementary Information adopted on 15.11.2018.

5.1.3. Imnovid - pomalidomide - Orphan - EMEA/H/C/002682/II/0031/G

Celgene Europe BV

Rapporteur: Greg Markey, Co-Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Patrick Batty

Scope: "Extension of indication to include treatment with Imnovid in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide; as a result, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. As a consequence the MAH submitted a request to add 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg Imnovid strengths to support the proposed posology and pomalidomide dose modification. The SmPC, Labelling and Package leaflet are updated in accordance. Update of section 5.1 of the SmPC in order to update the information on pomalidomide mechanism of action based on literature data."

Action: For adoption

Request for Supplementary Information adopted on 28.02.2019, 18.10.2018.

5.1.4. Keytruda - pembrolizumab - EMEA/H/C/003820/II/0057

Merck Sharp & Dohme B.V.

Rapporteur: Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Menno van der Elst

Scope: "Extension of indication to include 1st line treatment of locally advanced or metastatic non-small cell lung cancer tumours expressing PD-L1 with a ≥ 1% tumour proportion score (TPS), based on data from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC, and on supportive data from the final planned analysis of KEYNOTE-024; a Phase 3 randomized open-label study of KEYTRUDA monotherapy compared to platinum-based chemotherapy in metastatic NSCLC with PD-L1 TPS ≥50%. As a result, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. An updated RMP version 18.1 was provided as part of the application."

Action: For adoption

Request for Supplementary Information adopted on 18.10.2018.

5.1.5. Keytruda - pembrolizumab - EMEA/H/C/003820/II/0065

Merck Sharp & Dohme B.V.

Rapporteur: Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Menno van der Elst

Scope: "Extension of indication to include, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) Chemotherapy, first-line treatment of recurrent or metastatic head

and neck squamous cell carcinoma (HNSCC) in adults for Keytruda; based on the results from KEYNOTE-048, a randomized, multi-center, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated version of the RMP (Version 22.1) is also being submitted."

Action: For adoption

5.1.6. Mozobil - plerixafor - Orphan - EMEA/H/C/001030/II/0034

Genzyme Europe BV

Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Menno van der Elst

Scope: "Extension of indication to include paediatric patients aged 1 to 18 years for Mozobil. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance."

Action: For adoption

Request for Supplementary Information adopted on 28.02.2019, 13.12.2018, 31.05.2018.

5.1.7. Opsumit - macitentan - Orphan - EMEA/H/C/002697/II/0029

Janssen-Cilag International N.V.

Rapporteur: Concepcion Prieto Yerro, Co-Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Eva A. Segovia

Scope: "Extension of indication to include treatment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), based on the pivotal study MERIT-1 (AC-055E201), together with 6 months of efficacy and safety data (cut-off date 17 October 2017) from its ongoing open-label extension study MERIT-2 (AC-055E202), as well as a drug-drug interaction (DDI) study (AC-055-122) of macitentan and rosuvastatine, a DDI study (AC-055-123) of macitentan and riociguat, and observational data from the OPUS Registry (OPsumit USers Registry; cut-off date of 17 April 2018).
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 are being updated and the Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to implement editorial changes and to align the annexes with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet.
An updated RMP version 9.2 was provided as part of the application."

Action: For adoption

Request for Supplementary Information adopted on 13.12.2018.

5.1.8. Revlimid - lenalidomide - Orphan - EMEA/H/C/000717/II/0102/G

Celgene Europe BV

Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni

Scope: "Extension of indication to include treatment with Revlimid in combination with bortezomib and dexamethasone of adult patients with previously untreated multiple myeloma.

As a consequence, the MAH submitted a request to add 7-capsule pack sizes for the 7.5 mg, 20 mg and 25 mg strengths of Revlimid (lenalidomide) to support the proposed posology and lenalidomide dose modification. Sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated; the Package Leaflet is updated in accordance. Additionally, minor editorial changes have been introduced throughout the PI and annex II key elements of the RMM have been updated to include information on timing of blood and semen donation in line with the SmPC section 4.4.
An updated RMP (version 36.1) has also been submitted."

Oral explanation to be held on 26 March 2019 at time 09:00

Action: For adoption

Request for Supplementary Information adopted on 15.11.2018.

See 2.3

5.1.9. Victoza - liraglutide - EMEA/H/C/001026/II/0049

Novo Nordisk A/S

Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Menno van der Elst

Scope: "Extension of indication to include treatment of children and adolescents (age 10-17 years) with T2D based on Study NN2211-1800; a Phase 1 clinical pharmacology, multi-centre, randomised, double-blind placebo controlled trial, and Study NN2211-3659; a Phase 3a efficacy and safety, multi-centre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 5.2 of the SmPC are being updated and the Package Leaflet is updated accordingly.
Additionally, in accordance with the guideline from 2017 about excipients, the MAH took the opportunity to include sodium in SmPC section 4.4 and the Package Leaflet.
An updated RMP version 30 was provided as part of the application."

Action: For adoption

5.1.10. Zerbaxa - ceftolozane / tazobactam - EMEA/H/C/003772/II/0020

Merck Sharp & Dohme B.V.

Rapporteur: Bjorg Bolstad, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Adam Przybylkowski

Scope: "Extension of indication to include treatment of Nosocomial pneumonia, including ventilator associated pneumonia for Zerbaxa, based on results from the randomised, double-blind, multicentre clinical trial CXA-NP-11-04 (PN008).
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance (sections 1, 2, 3, 4 and 6).
The Applicant also took the opportunity to implement editorial changes in section 5.2 of the SmPC and to bring Section 4.4 of the SmPC and section 2 of the PL in line with the latest Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.
Version 2.1 of the RMP was also submitted."

Action: For adoption

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

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

6.1.1. human fibrinogen / human thrombin - EMEA/H/D/004308

to support the endogenous clotting process and increase of haemostasis in surgical procedures

Scope: List of outstanding issues

Action: For adoption

List of Questions adopted on 22.03.2018.

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

8.1.1. masitinib mesylate –Orphan - H0005118

AB Science, in combination with riluzole is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)

Scope: Briefing note and the Rapporteurs' recommendation on the request for accelerated assessment.

Action: For adoption

8.1.2. Obiltoxaximab - Orphan - H0005169

SFL Regulatory Services GmbH; is indicated in adults and paediatric patients for the treatment of inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs. is also indicated in adults and paediatric patients for the post-exposure prophylaxis of inhalation anthrax when alternative therapies are not appropriate or are not available.

Scope: Briefing note and the Rapporteurs' recommendation on the request for accelerated assessment.

Action: For adoption

8.2. Priority Medicines (PRIME)

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

8.2.1. List of applications received

Action: For information

8.2.2. Recommendation for PRIME eligibility

Action: For adoption

9. Post-authorisation issues

9.1. Post-authorisation issues

9.1.1. Adenuric - febuxostat - EMEA/H/C/000777/II/0051

Menarini International Operations Luxembourg S.A.,

Rapporteur: Andrea Laslop

Scope: "Update of section 5.1 of the SmPC in order to include the results of the clinical safety study CARES (TMX-67_301), to compare the cardiovascular outcomes of febuxostat and allopurinol in subjects with gout and cardiovascular comorbidities; this is a Multicenter, Randomized, Active-Control, Phase 3B Study.

In addition, the Marketing authorisation holder (MAH) took the opportunity to provide a consolidated Module 2.7.6 in order to list all the synopsis of individual studies in a unique tabular format."

Action: For discussion

Request for Supplementary Information adopted on 13.12.2018, 04.10.2018.

9.1.2. Busulfan Fresenius Kabi - busulfan - EMEA/H/C/002806/R/0010

Fresenius Kabi Deutschland GmbH, Generic of Busilvex

Rapporteur: John Joseph Borg, PRAC Rapporteur: Eva A. Segovia

Scope: Request for Supplementary Information

Action: For adoption

9.1.3. Fabrazyme - Agalsidase Beta - EMEA/H/C/000370

Genzyme Europe BV; treatment of Fabry disease

Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Outi Mäki-Ikola

Scope: Fabry disease registry – MAH responses to assessment of biennial report (MEA 57.9) concluding that the registry is currently insufficient to provide reliable information on long-term treatment

Action: For discussion

9.1.4. Fotivda - tivozanib - EMEA/H/C/004131

EUSA PHARMA; treatment of adult patients with advanced renal cell carcinoma (RCC)

Rapporteur: Bruno Sepodes, Co-Rapporteur: Greg Markey

Scope: Update on results from a phase 3 study, study AV-951-15-303 (TIVO-3) conducted in patients with advanced refractory RCC who have failed 2-3 prior systemic therapies.

Action: For adoption

9.1.5. NINLARO - ixazomib - EMEA/H/C/003844/II/0014/G, Orphan

Takeda Pharma A/S

Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Annika Folin

Scope: “Group of variations consisting of a type 2 variation to include submission of final report of progression free survival (PFS) in fulfilment of SOB004 and a type IB variation to request an extension of the due date of SOB003. Annex II is amended accordingly. Consequently the RMP is updated (version 4.0).”

Action: For discussion

9.1.6. Pixuvri - pixantrone - EMEA/H/C/002055/R/0046

CTI Life Sciences Limited

Rapporteur: Tuomo Lapveteläinen, Co-Rapporteur: Filip Josephson

Scope: Request for Supplementary Information

Action: For adoption

9.1.7. Zejula - niraparib - EMEA/H/C/004249/II/0006, Orphan

Tesaro Bio Netherlands B.V.

Rapporteur: Bjorg Bolstad, PRAC Rapporteur: Jan Neuhauser

Scope: “Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to optimise the starting dose of niraparib and clarify dose modification information, modify the existing warning on haematologic adverse reactions, amend the description of thrombocytopenia and amend existing efficacy and pharmacokinetics information, respectively. The changes are

based on the integrated population clinical report that contains information from the completed Phase 3 NOVA, study submitted as part of the initial MAA, as well as supportive information from the ongoing phase 2 PR-30-5020-C (QUADRA) and phase 1 / 2 300-PN-162-01-001 (TOPACIO) studies. The update of the SmPC posology is based on exposure response study reports to propose alternative dosing strategies that aim to reduce Grade 3/4 thrombocytopenia; the Package Leaflet is updated accordingly. The RMP version 1.1 has also been submitted to reflect the new EU RMP format. Furthermore, the core sections of the RMP have been updated to: align with niraparib PSUR 1, reflect post-authorization experience, inclusion of embolic and thrombotic events as important potential risks and to optimize the starting dose of niraparib to reduce adverse events.",

Action: For adoption

Request for Supplementary Information adopted on 29.11.2018.

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

10.5.1. Septanest and associated names - articaine (hydrochloride)/adrenaline (tartare) - EMEA/H/A-30/1461

MAH Septodont group of companies and associated companies

Rapporteur: Romaldas Maciulaitis, Co-rapporteur: Fatima Ventura

Scope: Opinion

Action: For adoption

Harmonisation exercise for Septanest and associated names. Summary of Product Characteristics and Module 3 harmonisation was triggered by the MAH.

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

10.6.1. Omega-3-acid-ethyl esters- containing medicinal products for oral use – EMEA/H/A-31/1464

MAHs: various

Re-examination Rapporteur: John Joseph Borg, Re-examination Co-Rapporteur: Johann Lodewijk Hillege

Scope: Oral Explanation on Re-examination, SAG Report

Oral explanation to be held on 27 March 2019 at time 15:30

Action: For adoption

Review of the benefit-risk balance following notification by the MPA in Sweden on 15 March 2018 of a referral under Article 31 of Directive 2001/83/EC.

See 2.4

10.6.2. Fosfomycin containing medicinal products – EMEA/H/A-31/1476

MAH various

Rapporteur: Ondrej Slanar, Co-rapporteur: Janet Koenig

Scope: List of outstanding issues

Action: For adoption

Need to re-evaluate the benefit-risk ratio of the approved indications considering the current scientific knowledge. Furthermore, the appropriate dose and duration of administration for both oral and intravenous formulations need to be discussed as well as the adequacy of safety relevant information and information about pharmacological properties.

The German National Competent Authority triggered a referral under Article 31 of Directive 2001/83 based on interest of the Union, requesting an opinion to CHMP on the benefit-risk of fosfomycin-containing products and on the need for regulatory measures to be taken.

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

10.11.1. Basiron AC – benzoyl peroxide, hydrous – EMEA/H/A-13/1475

MAHs: Galderma Nordic AB

Rapporteur: Filip Josephson, Co-Rapporteur: Johann Lodewijk Hillege

Scope: Opinion

Action: For adoption

This procedure concerns a Type II Quality WS variation (SE/H/xxxx/WS/190). The notification received by the reference member state (SE) on 26/10/2018, notifying of the start of a referral under Article 13 of Commission regulation (EC) No 1234/2008.

11. Pharmacovigilance issue

11.1. Early Notification System

March 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

14.2.1. Handling of confidential information within the EU network

Action: For discussion

14.2.2. Pharmacovigilance Risk Assessment Committee (PRAC)

Summary of recommendations and advice of PRAC meeting held on 12-15 March 2019

Action: For information

List of Union Reference Dates and frequency of submission of Periodic Safety Update Reports (EURD list) for March 2019

Action: For adoption

14.2.3. Committee for Advanced Therapies (CAT)

CAT draft minutes of meeting held on 20-22 March 2019
Action: For information

14.2.4. Paediatric Committee (PDCO)

PIPs reaching D30 at March 2019 PDCO

Action: For information

Report from the PDCO meeting held on 26-29 March 2019

Action: For information

14.2.5. Committee for Orphan Medicinal Products (COMP)

Report from the COMP meeting held on 19-21 March 2019
Action: For information

14.2.6. Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

Report from the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on the meeting held on 26-28 March 2019

Action: For information

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

14.3.1. Ad-hoc Influenza Working Group

Scope: EU Strain selection for the Influenza Vaccines for the Season 2019/2020: Report from the Ad Hoc Influenza working group to the BWP

Action: For adoption

Scope: EU Recommendation for the Seasonal Influenza Vaccine Composition for the Season 2019/2020

Action: For adoption

14.3.2. Biologics Working Party (BWP)

Chair: Sol Ruiz/Nanna Aaby Kruse,

Reports from BWP March 2019 meeting to CHMP for adoption:

- 18 reports on products in scientific advice and protocol assistance
- 8 reports on products in pre-authorisation procedures
- 3 reports on products in post-authorisation procedures
- 2 reports on products in plasma master file

Action: For adoption

14.3.3. Name Review Group (NRG)

Scope: Recommendation to CHMP

Action: For adoption

14.3.4. Scientific Advice Working Party (SAWP)

Chair: Anja Schiel

Improvement of organisational aspects of SAWP/CHMP collaboration

Action: For information

Report from the SAWP meeting held on 12-15 March 2019. Table of conclusions

Action: For information

Scientific advice letters: Disclosure of information related to scientific advice letters cannot be released at present time as these contain commercially confidential information.

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

14.8.1. Update of the Business Pipeline report for the human scientific committees

2019 initial marketing authorisation application submissions with eligibility request to central procedure

Action: For information

14.9. Others

No items

15. Any other business

15.1. AOB topic

15.1.1. Health & Safety induction

SPARK building: Health and Safety induction

Action: For information

16. 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)*

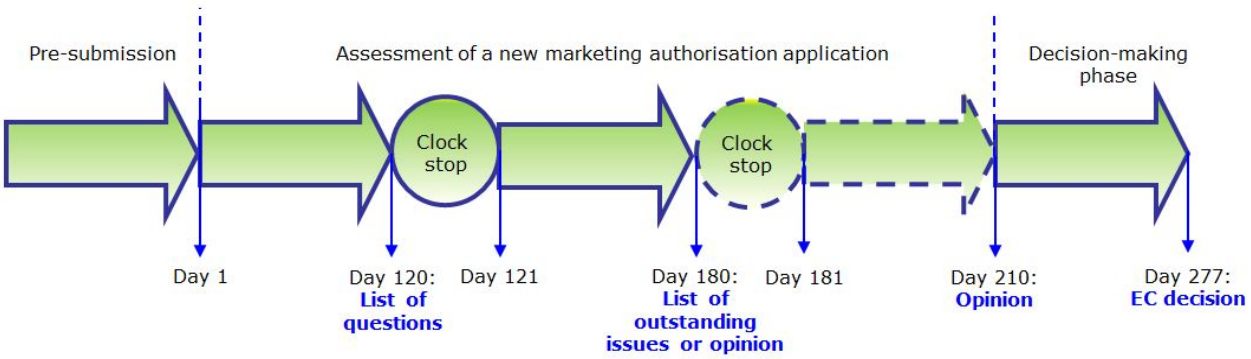
The items listed in this section are those for which marketing authorisation holders (MAHs) or applicants have been invited to the CHMP plenary meeting to address questions raised by the Committee. Oral explanations normally relate to on-going applications (section 3, 4 and 5) or referral procedures (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 *(section5.3)*

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 Pharmamacovigilance 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/

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2019
EMA/CHMP/191423/2019

Annex to 25-28 March 2019 CHMP Agenda

Pre-submission and post-authorisations issues

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A. PRE SUBMISSION ISSUES

A.1. ELIGIBILITY REQUESTS

Report on Eligibility to Centralised Procedure for March 2019: **For adoption**

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

Final Outcome of Rapporteurship allocation for March 2019: **For adoption**

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

Defitelio - defibrotide -
EMEA/H/C/002393/S/0038, Orphan
Gentium S.r.l., Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga

Vyndaqel - tafamidis -
EMEA/H/C/002294/S/0047, Orphan
Pfizer Europe MA EEIG, Rapporteur: Joseph Emmerich, PRAC Rapporteur: Ghania Chamouni

B.2. RENEWALS OF MARKETING AUTHORISATIONS OUTCOMES

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

Envarsus - tacrolimus -
EMEA/H/C/002655/R/0014
Chiesi Farmaceutici S.p.A., Rapporteur: John Joseph Borg, PRAC Rapporteur: Ronan Grimes
Request for Supplementary Information adopted on 31.01.2019.

B.2.2. Renewals of Marketing Authorisations for unlimited validity

Abasaglar - insulin glargine -
EMEA/H/C/002835/R/0023
Eli Lilly Nederland B.V., Rapporteur: Kristina

Dunder, Co-Rapporteur: Agnes Gyurasics, PRAC Rapporteur: Amelia Cupelli

ILARIS - canakinumab - EMEA/H/C/001109/R/0062
Novartis Europharm Limited, Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Brigitte Keller-Stanislawski

Orphacol – Cholic Acid - EMEA/H/C/001250/R/0028
Laboratoires CTRS, Rapporteur: Constantinos Markopoulos, Co-Rapporteur: Peter Kiley, PRAC Rapporteur: Sophia Trantza

VIZAMYL - flutemetamol (18F) - EMEA/H/C/002557/R/0017
GE Healthcare AS, Rapporteur: Concepcion Prieto Yerro, Co-Rapporteur: Janet Koenig, PRAC Rapporteur: Martin Huber

Xultophy - insulin degludec / liraglutide - EMEA/H/C/002647/R/0028
Novo Nordisk A/S, Rapporteur: Kristina Dunder, Co-Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Menno van der Elst

B.2.3. Renewals of Conditional Marketing Authorisations

Pixuvri - pixantrone - EMEA/H/C/002055/R/0046
CTI Life Sciences Deutschland GmbH, Rapporteur: Outi Mäki-Ikola, Co-Rapporteur: Filip Josephson, PRAC Rapporteur: Kirsti Villikka
Request for Supplementary Information adopted on 31.01.2019.

See 9.1

B.3. POST-AUTHORISATION PHARMACOVIGILANCE OUTCOMES

Signal detection

PRAC recommendations on signals adopted at the PRAC meeting held on 12-15 March 2019 PRAC:

Signal of hypoparathyroidism

OPDIVO - nivolumab – EMEA/H/C/003985
Bristol-Myers Squibb Pharma EEIG, Rapporteur: Jorge Camarero Jiménez, Co-Rapporteur: Paula Boudewina van Hennik

PRAC recommendation on a variation: **For adoption**

PSUR procedures for which PRAC adopted a recommendation for variation of the terms of the MA at its March 2019 meeting:
EMEA/H/C/PSUSA/00002417/201807 (glimepiride / pioglitazone hydrochloride, metformin / pioglitazone, pioglitazone) CAPS: **Actos** (EMEA/H/C/000285) (pioglitazone), Takeda Pharma A/S, Rapporteur: Peter Kiely **Competact** (EMEA/H/C/000655) (pioglitazone / metformin), Takeda Pharma A/S, Rapporteur: Peter Kiely **Glubrava** (EMEA/H/C/000893) (pioglitazone / metformin hydrochloride), Takeda Pharma A/S, Rapporteur: Peter Kiely **Glustin** (EMEA/H/C/000286) (pioglitazone), Takeda Pharma A/S, Rapporteur: Peter Kiely **Tandemact** (EMEA/H/C/000680) (pioglitazone / glimepiride), Takeda Pharma A/S, Rapporteur: Peter Kiely, PRAC Rapporteur: Rhea Fitzgerald, "01 August 2016 to 31 July 2018"
EMEA/H/C/PSUSA/00010084/201808 (dabrafenib) CAPS: **Tafinlar** (EMEA/H/C/002604) (dabrafenib), Novartis Europharm Limited, Rapporteur: Filip Josephson, PRAC Rapporteur: Annika Folin, "27/08/2017 - 26/08/2018"
EMEA/H/C/PSUSA/00010403/201809 (pembrolizumab) CAPS: **Keytruda** (EMEA/H/C/003820) (pembrolizumab), Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Menno van der Elst, "from 4 March 2018 to 3 September 2018"

B.4. EPARs / WPARs

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

Accofil - filgrastim - EMEA/H/C/003956/II/0028/G	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP

Accord Healthcare S.L.U., Rapporteur: Outi Mäki-Ikola Opinion adopted on 07.03.2019.	Members were in agreement with the CHMP recommendation.
Aimovig - erenumab - EMEA/H/C/004447/II/0003/G Novartis Europharm Limited, Rapporteur: Kristina Dunder	
Bemfola - follitropin alfa - EMEA/H/C/002615/II/0021/G Gedeon Richter Plc., Rapporteur: Paula Boudewina van Hennik Opinion adopted on 07.03.2019.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
BeneFIX - nonacog alfa - EMEA/H/C/000139/II/0156/G Pfizer Europe MA EEIG, Rapporteur: Jan Mueller-Berghaus	
Dupixent - dupilumab - EMEA/H/C/004390/II/0013/G sanofi-aventis groupe, Rapporteur: Jan Mueller-Berghaus Request for Supplementary Information adopted on 14.02.2019.	
Entyvio - vedolizumab - EMEA/H/C/002782/II/0038/G Takeda Pharma A/S, Rapporteur: Daniela Melchiorri Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Firazyr - icatibant - EMEA/H/C/000899/II/0046, Orphan Shire Pharmaceuticals Ireland Limited, Rapporteur: Kristina Dunder Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Flixabi - infliximab - EMEA/H/C/004020/II/0038 Samsung Bioepis NL B.V., Rapporteur: Jan Mueller-Berghaus Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Flucelvax Tetra - influenza vaccine surface antigen inactivated prepared in cell cultures - EMEA/H/C/004814/II/0003 Seqirus Netherlands B.V., Rapporteur: Sol Ruiz Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Foclivia - influenza virus surface antigens (inactivated) of strain	

A/Vietnam/1194/2004 (H5N1) - EMEA/H/C/001208/II/0040/G Seqirus S.r.l, Rapporteur: Daniela Melchiorri Request for Supplementary Information adopted on 07.02.2019.	
Herzuma - trastuzumab - EMEA/H/C/002575/II/0012 Celltrion Healthcare Hungary Kft., Rapporteur: Jan Mueller-Berghaus Request for Supplementary Information adopted on 15.11.2018.	
Humira - adalimumab - EMEA/H/C/000481/II/0184/G AbbVie Deutschland GmbH & Co. KG, Rapporteur: Kristina Dunder Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 07.02.2019, 06.12.2018.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Humira - adalimumab - EMEA/H/C/000481/II/0189 AbbVie Deutschland GmbH & Co. KG, Rapporteur: Kristina Dunder Opinion adopted on 07.03.2019.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Imfinzi - durvalumab - EMEA/H/C/004771/II/0003 AstraZeneca AB, Rapporteur: Sinan B. Sarac Opinion adopted on 07.03.2019. Request for Supplementary Information adopted on 17.01.2019.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Imraldi - adalimumab - EMEA/H/C/004279/II/0021 Samsung Bioepis NL B.V., Rapporteur: Outi Mäki-Ikola Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Jylamvo - methotrexate - EMEA/H/C/003756/II/0005/G Therakind Limited, Rapporteur: Bruno Sepodes	
Keytruda - pembrolizumab - EMEA/H/C/003820/II/0066/G Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 14.02.2019.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Lucentis - ranibizumab - EMEA/H/C/000715/II/0075/G	

Novartis Europharm Limited, Rapporteur: Kristina Dunder Request for Supplementary Information adopted on 24.01.2019.	
Mektovi - binimetinib - EMEA/H/C/004579/II/0002/G Pierre Fabre Medicament, Rapporteur: Janet Koenig	
Menveo - meningococcal group A, C, W135 and Y conjugate vaccine - EMEA/H/C/001095/II/0078/G GSK Vaccines S.r.l, Rapporteur: Johann Lodewijk Hillege Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 24.01.2019.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Myozyme - alglucosidase alfa - EMEA/H/C/000636/II/0072 Genzyme Europe BV, Co-Rapporteur: Koenraad Norga Opinion adopted on 21.03.2019.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
NovoSeven - eptacog alfa (activated) - EMEA/H/C/000074/II/0106 Novo Nordisk A/S, Rapporteur: Paula Boudewina van Hennik Request for Supplementary Information adopted on 07.03.2019, 20.09.2018.	Request for supplementary information adopted with a specific timetable.
Omidria - phenylephrine / ketorolac - EMEA/H/C/003702/II/0008/G Omeros London Limited, Rapporteur: Jayne Crowe Opinion adopted on 07.03.2019. Request for Supplementary Information adopted on 29.11.2018.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
OPDIVO - nivolumab - EMEA/H/C/003985/II/0061/G Bristol-Myers Squibb Pharma EEIG, Rapporteur: Jorge Camarero Jiménez Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Rixubis - nonacog gamma - EMEA/H/C/003771/II/0028 Baxalta Innovations GmbH, Rapporteur: Andrea Laslop Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Simponi - golimumab - EMEA/H/C/000992/II/0087/G	Request for supplementary information adopted with a specific timetable.

Janssen Biologics B.V., Rapporteur: Kristina Dunder Request for Supplementary Information adopted on 21.03.2019.	
Soliris - eculizumab - EMEA/H/C/000791/II/0104/G, Orphan Alexion Europe SAS, Rapporteur: Jorge Camarero Jiménez Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Synflorix - pneumococcal polysaccharide conjugate vaccine (adsorbed) - EMEA/H/C/000973/II/0131 GlaxoSmithkline Biologicals SA, Rapporteur: Kristina Dunder	
Synflorix - pneumococcal polysaccharide conjugate vaccine (adsorbed) - EMEA/H/C/000973/II/0132 GlaxoSmithkline Biologicals SA, Rapporteur: Kristina Dunder	
Trazimera - trastuzumab - EMEA/H/C/004463/II/0005 Pfizer Europe MA EEIG, Rapporteur: Jan Mueller-Berghaus Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 31.01.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Tremfya - guselkumab - EMEA/H/C/004271/II/0009/G Janssen-Cilag International N.V., Rapporteur: Agnes Gyurasics Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Trumenba - meningococcal group B vaccine (recombinant, adsorbed) - EMEA/H/C/004051/II/0016/G Pfizer Europe MA EEIG, Rapporteur: Johann Lodewijk Hillege Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
UDENYCA - pegfilgrastim - EMEA/H/C/004413/II/0001/G ERA Consulting GmbH, Rapporteur: Martina Weise	
WS1432 Ambirix-EMEA/H/C/000426/WS1432/0093 Twinrix Adult-EMEA/H/C/000112/	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

WS1432/0127 **Twinrix Paediatric-EMEA/H/C/000129/WS1432/0128** GlaxoSmithkline Biologicals SA, Lead Rapporteur: Greg Markey Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 17.01.2019, 08.11.2018.	
WS1464/G **Revatio-EMEA/H/C/000638/WS1464/0084/G** **Viagra-EMEA/H/C/000202/WS1464/0100/G** Pfizer Europe MA EEIG, Lead Rapporteur: Johann Lodewijk Hillege	
WS1502 **Fertavid-EMEA/H/C/001042/WS1502/0042** **Puregon-EMEA/H/C/000086/WS1502/0100** Merck Sharp & Dohme B.V., Lead Rapporteur: Nithyanandan Nagercoil Request for Supplementary Information adopted on 07.03.2019, 06.12.2018.	Request for supplementary information adopted with a specific timetable.
WS1524 **HyQvia-EMEA/H/C/002491/WS1524/0048** **Kiovig-EMEA/H/C/000628/WS1524/0090** Baxter AG, Lead Rapporteur: Jan Mueller-Berghaus Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
WS1530/G **Aflunov-EMEA/H/C/002094/WS1530/0045/G** **Foclivia-EMEA/H/C/001208/WS1530/0039/G** Seqirus S.r.l, Lead Rapporteur: Daniela Melchiorri Request for Supplementary Information adopted on 07.02.2019.	
WS1532 **Bexsero-EMEA/H/C/002333/WS1532/0075** **Menveo-EMEA/H/C/001095/WS1532/0082** GSK Vaccines S.r.l, Lead Rapporteur: Kristina Dunder	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Opinion adopted on 14.03.2019.	
WS1534 **Infanrix hexa-EMEA/H/C/000296/WS1534/0254** GlaxoSmithkline Biologicals SA, Lead Rapporteur: Bart Van der Schueren Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1548 **Abseamed-EMEA/H/C/000727/WS1548/0080** **Binocrit-EMEA/H/C/000725/WS1548/0080** **Epoetin alfa Hexal-EMEA/H/C/000726/WS1548/0079** Hexal AG, Duplicate, Duplicate of Binocrit, Lead Rapporteur: Alexandre Moreau Opinion adopted on 07.03.2019. Request for Supplementary Information adopted on 31.01.2019.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Hexacima-EMEA/H/C/002702/WS1496/0085/G **Hexaxim-EMEA/H/W/002495/WS1496/0090/G** **Hexyon-EMEA/H/C/002796/WS1496/0089/G** Sanofi Pasteur, Lead Rapporteur: Jan Mueller-Berghaus Request for Supplementary Information adopted on 24.01.2019.	

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

Adenuric - febuxostat - EMEA/H/C/000777/II/0051 Menarini International Operations Luxembourg S.A., Rapporteur: Andrea Laslop, “Update of section 5.1 of the SmPC in order to include the results of the clinical safety study CARES (TMX-67_301), to compare the cardiovascular outcomes of febuxostat and allopurinol in subjects with gout and cardiovascular comorbidities; this is a Multicenter, Randomized, Active-Control, Phase 3B Study. In addition, the Marketing authorisation holder (MAH) took the opportunity to provide a consolidated Module 2.7.6 in order to list all the synopsis of individual studies in a unique tabular format.” Request for Supplementary Information adopted	See agenda 9.1

on 13.12.2018, 04.10.2018.	
Apealea - paclitaxel - EMEA/H/C/004154/II/0001 Oasmia Pharmaceutical AB, Rapporteur: Bart Van der Schueren, "Update of section 5.1 of the SmPC in order to present post-hoc analyses of efficacy results for patients with first relapse in accordance with the approved indication. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor typographical errors in the SmPC." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Bexsero - meningococcal group b vaccine (recombinant, component, adsorbed) - EMEA/H/C/002333/II/0074 GSK Vaccines S.r.l, Rapporteur: Kristina Dunder, "Update of section 4.5 of the SmPC in order to include the possibility of concomitant administration with the MenACWY vaccine based on final results from study V72_56. This was a phase 3b study assessing the safety and immunogenicity of Bexsero administered concomitantly with MenACWY vaccine as compared to their individual administration in healthy infants at approximately 3, 5, 7 and 13 months of age. This submission constitutes follow-on to procedure EMEA/H/C/002333/P46/027. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes throughout the Product Information and Annex A." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Biktarvy - bictegravir / emtricitabine / tenofovir alafenamide - EMEA/H/C/004449/II/0011 Gilead Sciences Ireland UC, Rapporteur: Joseph Emmerich, "Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information based on the pooling of 96-week data from two randomized, double-blind, active controlled studies GS-US-380-1489 and GS-US-380-1490 in HIV-1 infected, antiretroviral treatment-naïve adults receiving Biktarvy compared with each of the comparator treatment groups (i.e. pooled Biktarvy (BVY) vs abacavir /dolutegravir /lamivudine and pooled BVY vs dolutegravir + emtricitabine/tenofovir	

alafenamide). In addition the Marketing authorisation holder (MAH) took the opportunity to introduce some minor linguistic amendments in the SmPC and the Package Leaflet”	
Bosulif - bosutinib - EMEA/H/C/002373/II/0036 Pfizer Europe MA EEIG, Rapporteur: Janet Koenig, “Submission of the analysis of the pop PK data as recommended by the CHMP.” Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Cerdelga - eliglustat - EMEA/H/C/003724/II/0021, Orphan Genzyme Europe BV, Rapporteur: Johann Lodewijk Hillege, “Submission of the final report from study PKM14281, A Randomized, Three-Period Crossover Study of Single and Repeated Doses for Three Different Strengths of Eliglustat in Healthy Adult, CYP2D6 Extensive and Poor Metabolizers, to characterize dose proportionality of 21, 42 and 84 mg eliglustat dosage strengths, in line with CHMP recommendation.” Request for Supplementary Information adopted on 21.03.2019.	Request for supplementary information adopted with a specific timetable.
Cerdelga - eliglustat - EMEA/H/C/003724/II/0021, Orphan Genzyme Europe BV, Rapporteur: Johann Lodewijk Hillege, “Submission of the final report from study PKM14281, A Randomized, Three-Period Crossover Study of Single and Repeated Doses for Three Different Strengths of Eliglustat in Healthy Adult, CYP2D6 Extensive and Poor Metabolizers, to characterize dose proportionality of 21, 42 and 84 mg eliglustat dosage strengths, in line with CHMP recommendation.”	
Cimzia - certolizumab pegol - EMEA/H/C/001037/II/0075 UCB Pharma S.A., Rapporteur: Kristina Dunder, “Update of section 4.1 of the SmPC to add more clarity to the axial spondyloarthritis (axSpA) indication statement in particular with regard to the terms radiographic versus non-radiographic axSpA and update of sections 4.8 and 5.1 of the SmPC to reflect the availability of additional safety information from the phase 3 clinical study designed to evaluate the safety and efficacy of	

certolizumab in subjects with active axSpA without X-ray evidence of ankylosing spondylitis and objective signs of inflammation (AS0006)"	
Cyramza - ramucirumab - EMEA/H/C/002829/II/0029 Eli Lilly Nederland B.V., Rapporteur: Paula Boudewina van Hennik, "Submission of results of post-authorisation efficacy study (PAES): In order to investigate the potential correlation between biomarker measures (VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, additional KRAS, NRAS and BRAF mutations) and efficacy outcome (PFS, OS), the MAH should submit the results of a biomarker assay from the RAISE translational research population. Data presented corresponds with VEGF-C and VEGF-D biomarkers to complete the already submitted data for sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, KRAS, NRAS and BRAF mutations. As a result, Annex II of the product information is updated to remove this condition." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Dacogen - decitabine - EMEA/H/C/002221/II/0039, Orphan Janssen-Cilag International N.V., Rapporteur: Alexandre Moreau, "Update of the SmPC Section 4.8 to add "Hyperglycaemia" as a new adverse drug reaction. As a result of this addition, the SmPC section 5.1 was also revised. The Package leaflet is updated accordingly."	
Defitelio - defibrotide - EMEA/H/C/002393/II/0039, Orphan Gentium S.r.l., Rapporteur: Kristina Dunder, "Update of section 5.1 of the SmPC to amend the mechanism of action with new data on non-clinical studies identified from published literature." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Gilenya - fingolimod - EMEA/H/C/002202/II/0053 Novartis Europharm Limited, Rapporteur: Alexandre Moreau, "Type II (C.I.4): - to update section 4.4 of the SmPC (subsection 'Return of disease activity (rebound)' and subsection 'Stopping therapy') to add information to prescriber's on the timing of reported events and further recommendations on monitoring of	Request for supplementary information adopted with a specific timetable.

patients. - to update section 4.6 of the SmPC to add a warning for women stopping treatment for the purpose of becoming pregnant and for pregnant women, and addition of a cross-reference to section 4.4 subsection 'Return of disease activity (rebound)'. - to update section 4.8 of the SmPC to add a new adverse reaction 'Severe exacerbation of disease after Gilenya discontinuation' with frequency 'Not known'. The package leaflet is updated accordingly." Request for Supplementary Information adopted on 07.03.2019.	
Humira - adalimumab - EMEA/H/C/000481/II/0187 AbbVie Deutschland GmbH & Co. KG, Rapporteur: Kristina Dunder, "Submission of the final report from study M11-327: A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis; listed as a category 3 study in the RMP." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Imbruvica - ibrutinib - EMEA/H/C/003791/II/0048, Orphan Janssen-Cilag International NV, Rapporteur: Filip Josephson, "Update of section 4.4 of the SmPC Special warnings and precautions for use in order to add a warning under "bleeding-related events' based on the final clinical study reports results to evaluate the risks of major hemorrhage with the administration of IMBRUVICA (ibrutinib)). The study is listed in section III.2 additional Pharmacovigilance Activities A non-interventional PASS clinical study report (CSR) for serious haemorrhage in the RMP. In addition, the Marketing authorisation holder (MAH) took the opportunity to include a minor edit in the list of local representatives in the Package Leaflet." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Inflectra - infliximab - EMEA/H/C/002778/II/0072 Pfizer Europe MA EEIG, Duplicate, Duplicate of	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

Remsima, Rapporteur: Outi Mäki-Ikola, "Submission of the final study report of study CT-P13 4.1- An Open-label, Single-arm, Phase IV Study to Evaluate Safety and Efficacy of infliximab in Korean Patients with Inflammatory Bowel Disease." Opinion adopted on 14.03.2019.	recommendation.
INTELENCE - etravirine - EMEA/H/C/000900/II/0055 Janssen-Cilag International NV, Rapporteur: Joseph Emmerich, "Update of sections 4.4 and 4.8 of the SmPC to include the information that a higher incidence of Stevens-Johnson Syndrome (SJS) has been observed in children compared to the incidence reported in adult clinical trials, as assessed in the TMC125-EPPICC study submitted according to Art. 46 procedure (no. EMA/H/C/000900/P46/052). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make an amendment in section 4.2 of the SmPC by replacing the word "tablet" with "dose" in the missed dose information. The Package Leaflet is updated accordingly."	
Kanuma - sebelipase alfa - EMEA/H/C/004004/II/0019, Orphan Alexion Europe SAS, Rapporteur: Bart Van der Schueren, "Submission of the final report from study LAL-CL04, in order to fulfil this recommendation (REC). This is an open label multicentre extension study to evaluate the long-term safety, tolerability and efficacy of sebelipase alfa in adult subjects with liver dysfunction due to lysosomal acid lipase deficiency who previously received treatment in study LAL-CL01." Request for Supplementary Information adopted on 21.03.2019.	Request for supplementary information adopted with a specific timetable.
Lonquex - lipegfilgrastim - EMEA/H/C/002556/II/0048 Teva B.V., Rapporteur: Outi Mäki-Ikola, "Update of section 5.1 of the SmPC in order to include information based on results from study XM22-ONC-40041 listed as an imposed PASS in the Annex II; this is a multinational, multicentre, randomised, double-blind, placebo- and active-controlled study to further investigate the risks of disease progression and mortality	

associated with pegfilgrastim."	
Maviret - glecaprevir / pibrentasvir - EMEA/H/C/004430/II/0021 AbbVie Deutschland GmbH & Co. KG, Rapporteur: Joseph Emmerich, "Update of sections 4.8 and 5.1 of the SmPC in order to include results from the final study report for study M16-127 (EXPEDITION-5), a multicentre, open-label study to evaluate the efficacy and safety of glecaprevir/pibrentasvir in renally-impaired adults with chronic hepatitis C virus genotype 1-6 infection." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Mekinist - trametinib - EMEA/H/C/002643/II/0033 Novartis Europharm Limited, Rapporteur: Paula Boudewina van Hennik, "Update of section 4.6 of the SmPC in order to update information on Fertility, pregnancy and lactation after routine review of the company core data sheet, taking into consideration the original source documentation from GSK (former MAH), current scientific knowledge, published literature, as well as health authority and working group guidelines. The Package leaflet is being updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes in section 4.4 and 4.8 of the SmPC." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Menveo - meningococcal group A, C, W135 and Y conjugate vaccine - EMEA/H/C/001095/II/0083 GSK Vaccines S.r.l, Rapporteur: Johann Lodewijk Hillege, "Update of section 4.5 of the SmPC in order to include reference to concomitant administration with Meningococcal group B vaccine, based on results from study V72_56, previously submitted and assessed as part of procedure P46/035 for Menveo. The Package Leaflet (Section 2) is updated accordingly."	
Orfadin - nitisinone - EMEA/H/C/000555/II/0067 Swedish Orphan Biovitrum International AB, Rapporteur: Daniela Melchiorri, "Update of sections 4.4 and 4.5 to add a warning on interaction with medicinal products with a narrow	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

therapeutic window metabolized through CYP2C9 and information based on in vitro and in vivo drug drug interaction studies investigating effects of nitisinone on cytochromes CYP2C9, CYP1A2, CYP2B6, CYP3A4/5, P-gp, BCRP, OATP1B1, OATP1B3 or OCT2-mediated transport. The Package Leaflet is updated accordingly. This update is following PRAC conclusions on PSUSA (EMEA/H/CPSUSA/00002169/201802) adopted on 6 September 2018." Opinion adopted on 07.03.2019. Request for Supplementary Information adopted on 31.01.2019.	
Ozurdex - dexamethasone - EMEA/H/C/001140/II/0032 Allergan Pharmaceuticals Ireland, Rapporteur: Concepcion Prieto Yerro, "Update of section 4.4 of the SmPC in order to add warning on visual disturbance following the PRAC assessment outcome of EMEA/H/C/PSUSA/00000985/201801 procedure, the information for healthcare professionals has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives."	
Pradaxa - dabigatran etexilate - EMEA/H/C/000829/II/0114 Boehringer Ingelheim International GmbH, Rapporteur: Mark Ainsworth, "Update of section 5.1 of the SmPC based on the final results of the Graham et al. study; this is a non-interventional Medicare study in US patients over 65 years of age comparing patients initiating dabigatran or warfarin for the treatment of non-valvular atrial fibrillation. In addition, the Marketing authorisation holder (MAH) took the opportunity to make some corrections throughout the PI, update the contact details of the Austrian local representative in the package leaflet, to align section 2 of the package leaflet with section 4.3 of the SmPC and section 3 of the package leaflet with section 4.2 of the SmPC, and to make corrections to the Bulgarian and French translations." Request for Supplementary Information adopted on 31.01.2019.	
PREVYMIS - letermovir - EMEA/H/C/004536/II/0009, Orphan Merck Sharp & Dohme B.V., Rapporteur: Filip	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

Josephson, “Update of section 4.5 of the SmPC in order to update the information on drug-drug interaction between letermovir and fluconazole based on the results from study MK-8228-037; this is an open-label, 3-period, fixed-sequence trial to evaluate the effect of single-dose administration of letermovir on the single-dose PK of fluconazole, and the effect of single dose administration of fluconazole on the single-dose PK of letermovir in healthy females. Moreover, the median time to maximum plasma concentration was updated in section 5.2 of the SmPC. In addition, the Marketing authorisation holder (MAH) took the opportunity include minor editorial changes in the SmPC and package leaflet.” Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 17.01.2019.	recommendation.
Ranexa - ranolazine - EMEA/H/C/000805/II/0057/G Menarini International Operations Luxembourg S.A., Rapporteur: Kristina Dunder, “Grouping of 4 type II variations to update sections 4.6 and 5.3 of the SmPC based on the final results from 4 new non-clinical studies (studies TX-259-2004, 2005, 2006 and 2007); study TX-259-2006 is an oral (gavage) study of the effects of ranolazine on fertility and early embryonic development to implantation in rats, study TX-259-2004: An oral (Gavage) study of the effects of ranolazine on embryo/foetal development in rabbits, study TX-259-2005: An oral (Gavage) study of the effects of ranolazine on embryo/foetal development in rats and study TX-259-2007: An oral (Gavage) study of the effects of ranolazine on pre- and post-natal development including maternal function in rats. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement the warning on sodium salt in line with the revised annex to the EC guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ in section 2 of the package leaflet, and to update the contact details of the local representatives in Bulgaria, Slovenia and the Slovak republic in the Package Leaflet.”	
Remsima - infliximab - EMEA/H/C/002576/II/0063	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP

Celltrion Healthcare Hungary Kft., Rapporteur: Outi Mäki-Ikola, “Submission of the final study report of study CT-P13 4.1- An Open-label, Single-arm, Phase IV Study to Evaluate Safety and Efficacy of infliximab in Korean Patients with Inflammatory Bowel Disease.” Opinion adopted on 14.03.2019.	Members were in agreement with the CHMP recommendation.
Repatha - evolocumab - EMEA/H/C/003766/II/0031 Amgen Europe B.V., Rapporteur: Johann Lodewijk Hillege, “Update of section 5.1 of the SmPC based on the final results from study 20110271 (TAUSSIG) listed as a category 3 study in the RMP, submitted in order to fulfil MEA 003 and article 46 of Regulation EC No 1901/2006; this is a multicenter, open-label study to assess the long-term safety, tolerability and efficacy of AMG 145 (evolocumab) on LDL-C in adult and adolescent subjects with severe familial hypercholesterolemic (FH), including subjects with homozygous familial hypercholesterolemia (HoFH). In addition, the Marketing authorisation holder (MAH) took the opportunity to make a correction to the Labelling.”	
Ryzodeg - insulin aspart / insulin degludec - EMEA/H/C/002499/II/0030/G Novo Nordisk A/S, Rapporteur: Kristina Dunder, “Update of sections 4.2 and section 5.1 of the SmPC in order to update the information on dosing and administration interval of Ryzodeg (insulin aspart/insulin degludec) based on data from 2 trials: • NN5401-4266, a 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification. • NN5401-3996, a 26-week trial comparing efficacy and safety of insulin degludec/insulin aspart BID and insulin degludec OD plus insulin aspart in subjects with type 2 Diabetes Mellitus treated with basal insulin in need of treatment intensification with mealtime insulin. In addition, the MAH took the opportunity to make editorial changes in the SmPC.” Request for Supplementary Information adopted on 31.01.2019.	
Shingrix - herpes zoster vaccine	Request for supplementary information adopted

(recombinant, adjuvanted) - EMEA/H/C/004336/II/0012 GlaxoSmithkline Biologicals SA, Rapporteur: Bart Van der Schueren, “Update of section 4.8 of the SmPC in order to add "hypersensitivity reactions including rash, urticaria and angioedema" as an adverse drug reaction with frequency "rare". This update is based on data from clinical trials, literature and post-marketing surveillance reports. The Package Leaflet is updated accordingly.” Request for Supplementary Information adopted on 14.03.2019.	with a specific timetable.
Skilarence - dimethyl fumarate - EMEA/H/C/002157/II/0008/G Almirall S.A, Rapporteur: Greg Markey, “Submission of the final report from study AML/27. This is an in vitro study aimed to assess the potential of dimethyl fumarate to inhibit human hepatic cytochrome P450 (CYP) enzymes. Submission of the final report from study AML/28. This is an in vitro study aimed to assess the potential interaction of dimethyl fumarate with p-glycoprotein (P-gp). Submission of the final report from study Almirall-15-05May2017. This is an in vitro study aimed to assess the interaction of dimethyl fumarate with human BCRP efflux (ABC) transporters.” Request for Supplementary Information adopted on 17.01.2019, 13.09.2018.	
Sprycel - dasatinib - EMEA/H/C/000709/II/0064 Bristol-Myers Squibb Pharma EEIG, Rapporteur: Sinan B. Sarac, “Submission of results from existing and new PK analyses together with the review of the literature data on the dasatinib PK profile in fasted conditions to assess implications arising for the recommendation for administration, as requested by the CHMP.” Request for Supplementary Information adopted on 15.11.2018.	
Tafinlar - dabrafenib - EMEA/H/C/002604/II/0038 Novartis Europharm Limited, Rapporteur: Filip Josephson, “Update of section 4.6 of the SmPC in order to update information on Fertility, pregnancy and lactation after routine review of the company core data sheet, taking into	Request for supplementary information adopted with a specific timetable.

consideration the original source documentation from GSK (former MAH), current scientific knowledge, published literature, as well as health authority and working group guidelines. The Package leaflet is being updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes in section 4.4 and 4.8 of the SmPC and in section 4 of the package leaflet." Request for Supplementary Information adopted on 14.03.2019.	
Tremfya - guselkumab - EMEA/H/C/004271/II/0010 Janssen-Cilag International N.V., Rapporteur: Agnes Gyurasics, "Update of sections 4.8 and 5.1 of the SmPC to add the long term 3-year clinical data from the two ongoing clinical studies CNTO1959PSO3001 (VOYAGE 1) and CNTO1959PSO3002 (VOYAGE 2) in subjects with plaque psoriasis." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Veltassa - patiromer - EMEA/H/C/004180/II/0007 Vifor Fresenius Medical Care Renal Pharma France, Rapporteur: Jayne Crowe, "Update of section 4.2, 4.5 and 5.1 of the SmPC to reflect the results of study RLY5016-401;an Open-Label, Randomized, Parallel Group Phase 4 Study of the Efficacy and Safety of Patiromer for Oral Suspension With or Without Food for the Treatment of Hyperkalemia (TOURMALINE). The PL has been updated accordingly." Request for Supplementary Information adopted on 14.03.2019, 17.01.2019.	Request for supplementary information adopted with a specific timetable.
Xeloda - capecitabine - EMEA/H/C/000316/II/0081 Roche Registration GmbH, Rapporteur: Janet Koenig, "Update of sections 4.2 and 4.8 of the SmPC in order to update the safety information with an adverse drug reactions that may occur upon accidental exposure to Xeloda crushed or cut tablets. The Package Leaflet is updated accordingly. In addition, the MAH is taking the opportunity to make some editorial changes to the Product Information."	
Xermelo - telotristat ethyl - EMEA/H/C/003937/II/0005, Orphan	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP

Ipsen Pharma, Rapporteur: Janet Koenig, "Update of section 5.2 of the SmPC in order to add information from an in vivo drug interaction study (study identifier: LX1606.1-110-NRM) to evaluate the effect of multiple doses of concomitant gastric acid reducers such as PPIs on the PK of telotristat ethyl, LP-778902." Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 24.01.2019, 15.11.2018.	Members were in agreement with the CHMP recommendation.
Xermelo - telotristat ethyl - EMEA/H/C/003937/II/0010, Orphan Ipsen Pharma, Rapporteur: Janet Koenig, "Update of section 5.3 of the SmPC in order to add information on carcinogenicity based on final results from study 8273113 (104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with LX1606 in Rats). The MAH took also the occasion to introduce some editorial changes in section 5.3 of the SmPC in alignment with the QRD wording." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Zebinix - eslicarbazepine acetate - EMEA/H/C/000988/II/0069 Bial - Portela & Cª, S.A., Rapporteur: Martina Weise, "Update of section 4.2 of the SmPC in order to update information related to the switch of tablet and suspension formulation based on the final results from study IA-2093-132, a pharmacokinetic study conducted to address the post-approval commitment: to compare the pharmacokinetic profile of the oral suspension versus the tablets."	
Zinforo - ceftaroline fosamil - EMEA/H/C/002252/II/0038 Pfizer Ireland Pharmaceuticals, Rapporteur: Greg Markey, "Update of section 4.2 of the SmPC to amend the recommended duration of ceftaroline fosamil intravenous (IV) infusion for standard dose regimens in adults and paediatrics to a range of 5 to 60 minutes from the currently recommended infusion duration of 1 hour. The PIL is updated accordingly. In addition the MAH has also taken the opportunity to reformat section 4.2 of the SmPC Posology and method of administration and to incorporate minor editorial updates to sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC." Request for Supplementary Information adopted	

on 20.09.2018.	
Zoely - nomegestrol acetate / estradiol - EMEA/H/C/001213/II/0049 Theramex Ireland Limited, Rapporteur: Joseph Emmerich, “Update of section 4.4 the SmPC in order to add a warning based on new data emerged from literature (as a follow up of a CCDS update) regarding a known association between hormonal contraceptives and a small increase in breast cancer (SDA 12). The Package Leaflet is updated accordingly.”	
Zydelig - idelalisib - EMEA/H/C/003843/II/0044 Gilead Sciences Ireland UC, Rapporteur: Filip Josephson, “Submission of the final clinical study report from study 101-99, A phase 1/2 extension study to investigate the safety and durability of clinical activity of CAL-101 in patients with hematologic malignancies, listed as category 1 commitment in the Risk Management Plan of Idelalisib and a post-authorisation measure listed within Annex IID of the product information (ANX 002). The product information annex IID has been updated.” Opinion adopted on 21.03.2019.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Zydelig - idelalisib - EMEA/H/C/003843/II/0045 Gilead Sciences Ireland UC, Rapporteur: Filip Josephson, “Submission of the final clinical study report for Phase 3 extension study GS US 312 0117, to evaluate the efficacy and safety of idelalisib (GS 1101) in combination with rituximab for previously treated CLL for patients with or without 17p deletion/TP53 mutation. This is a category 1 imposed pharmacovigilance activity, listed on the Risk Management Plan and is a post-authorisation measure listed within Annex IID of the product information (ANX 001). The product information annex IID has been updated.”	
WS1451 **Keppra-EMEA/H/C/000277/WS1451/0173** UCB Pharma S.A., Lead Rapporteur: Koenraad Norga, “Update of section 4.8 of the SmPC in order to add delirium (with frequency unknown) as adverse drug reaction based on results of category 4 . In addition, the Worksharing applicant (WSA)	

took the opportunity to correct a typological error in section 4.2: addition of equals sign in creatinine clearance values equal to or above 80 ml/min/1.73 m2. The Labelling is updated in accordance." Request for Supplementary Information adopted on 24.01.2019.	
WS1477 **Lixiana-EMEA/H/C/002629/WS1477/0019** **Roteas-EMEA/H/C/004339/WS1477/0007** Daiichi Sankyo Europe GmbH, Lead Rapporteur: Concepcion Prieto Yerro, "Update of sections 4.4, 4.8 and 5.1 of the SmPC for Lixiana and Roteas to update the clinical efficacy and safety information based on the final results from study DUI176b-D-U311, a phase IIIB prospective, randomised, open-label, blinded evaluator study to evaluate the efficacy and safety of low molecular weight heparin/edoxaban versus dalterparin in venous thromboembolism associated with cancer. In addition, the Worksharing applicant (WSA) took the opportunity to combine the 15 mg, 30 mg and 60 mg strengths SmPCs, to delete 'aspirin' from section 2 of the Package Leaflet, to update the contact details of the Portuguese local representative in the Package Leaflet for Lixiana only, and to make some corrections to the German, Finnish, Italian, Lithuanian, Maltese and Portuguese translations." Request for Supplementary Information adopted on 08.11.2018.	
WS1511/G **Advagraf-EMEA/H/C/000712/WS1511/0052/G** **Modigraf-EMEA/H/C/000954/WS1511/0031/G** Astellas Pharma Europe B.V., Lead Rapporteur: Jayne Crowe, "Update of sections 4.5 and 4.8 of the SmPC to add the drug-drug interaction with letemovir and to add the febrile neutropenia with frequency unknown, based on the cumulative review of the MAH safety database. Update of section 4.6 of the SmPC to add the information on pregnancy and lactation following the cumulative review of the cases reported in the MAH global safety database, published literature and the transplantation pregnancy exposure registry. The Package Leaflet is updated accordingly. In	Request for supplementary information adopted with a specific timetable.

addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes throughout the PI and to implement the wording from the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'."
Request for Supplementary Information adopted on 14.03.2019.

WS1544
Prezista-EMEA/H/C/000707/WS1544/0101
Rezolsta-EMEA/H/C/002819/WS1544/0030
Symtuza-EMEA/H/C/004391/WS1544/0016
Janssen-Cilag International NV, Lead Rapporteur: Johann Lodewijk Hillege, "Update of section 4.3 of the SmPC of Prezista, Rezolsta and Symtuza to contra-indicate the concomitant use with dapoxetine , domperidone, ivabradine and naloxegol , as well as to update section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with dapoxetine, domperidone, fesoterodine, irinotecan, ivabradine, naloxegol and solifenacin based on approved product information. The Package Leaflets are updated accordingly.
In addition, the Worksharing applicant (WSA) took the opportunity to update of section 3 of the SmPC of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling have been updated to reflect information on the in-use self-life in line with the approved Symtuza SmPC.
Moreover, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the Package Leaflet of Prezista and Rezolsta have been updated to include information on the sodium excipient."

Aluvia-EMEA/H/W/000764/WS1555/0107
Kaletra-EMEA/H/C/000368/WS1555/0175
Norvir-EMEA/H/C/000127/WS1555/0152
AbbVie Deutschland GmbH & Co. KG, Lead Rapporteur: Joseph Emmerich, "Update of sections 4.3 and 4.5 of the SmPC in order to add information on the contraindication and interaction between ritonavir and lomitapide based on a cumulative safety review of the SmPCs of protease inhibitors currently approved

for the treatment of HIV in the EU in combination with the pharmacokinetic enhancer (ritonavir), during the period from 1st August 2017 to 31st July 2018. This is in fulfilment of LEG 33.9. The Package Leaflets are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to correct a minor typographical error in the Norvir and Kaletra product information."	

B.5.3. CHMP-PRAC assessed procedures

Aranesp - darbepoetin alfa - EMEA/H/C/000332/II/0150 Amgen Europe B.V., Rapporteur: Martina Weise, PRAC Rapporteur: Martin Huber, "Update of the SmPC sections 4.4, 4.8, 5.1 based on the study data from Study 20070782 - a phase 3, randomized, double-blind, placebo-controlled, noninferiority study in subjects with chemotherapy-induced anemia receiving multi-cycle chemotherapy for the treatment of advanced stage nonsmall-cell lung cancer (NSCLC); study of epoetin alfa in metastatic breast cancer (EPO-ANE-3010) and the Company Core Data Sheet. In addition, the section 4.6 has been revised based on the recommendation from last Periodic Safety Update Report Number 33 dated 15 January 2018. Furthermore, the MAH took the opportunity to introduce minor editorial changes, update the information on local representatives and align the PI with the requirements of the QRD template 10.0. The PL is updated accordingly. The revised RMP version 9.3 has been also submitted."	
Benlysta - belimumab - EMEA/H/C/002015/II/0065 GlaxoSmithKline (Ireland) Limited, Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, "Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on suicidality and depression based on interim results from study BEL115467 listed in the Annex II; this is a Randomized, Double-Blind, Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab; the Package Leaflet is updated accordingly. The RMP	DHPC: increased risk for serious psychiatric events adopted on 14.03.2019. Adoption by written procedure on 18.03.2019.

version 30 has also been submitted. In addition, the Marketing authorisation holder (MAH) is proposing a DHPC letter and a communication plan."	
Champix - varenicline - EMEA/H/C/000699/II/0074 Pfizer Europe MA EEIG, Rapporteur: Mark Ainsworth, PRAC Rapporteur: Anette Kirstine Stark, "Update of sections 4.2, 5.1 and 5.2 of the SmPC to reflect results of the paediatric study A3051073 (MEA 047) " A Phase 4, Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study With Follow-Up, Evaluating The Safety And Efficacy Of Varenicline For Smoking Cessation In Healthy Adolescent Smokers." The PL is updated accordingly. RMP version 11.0 was submitted." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Esmya - ulipristal acetate - EMEA/H/C/002041/II/0045/G Gedeon Richter Plc., Rapporteur: Kristina Dunder, PRAC Rapporteur: Annika Folin, "Submission of the final study reports from the 5 mechanistic in vitro studies following Esmya Article 20 referral procedure (EMEA/H/A-20/1460/C/2041/0043). These are 3083-N03-050 (PAM MEA 020), 3083-N04-050 (PAM MEA 021), 3083-N05-050 (PAM MEA 022), 3083-N01-050 (PAM REC) and 3083-N02-050 (PAM REC). In addition, the MAH submitted updated RMP version 16.1, as part of this application." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 17.01.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Gardasil - human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - EMEA/H/C/000703/II/0080 MSD Vaccins, Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, "Update of sections 4.4 and 5.1 of the SmPC in order to update the information related to the effectiveness and immunogenicity of the immune response of Gardasil, based on the final results from the long-term follow-up of study V501-P015-21 listed as a category 3 study in the RMP; this study was designed to evaluate the effectiveness, immunogenicity and safety of the	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

quadrivalent human papillomavirus (qHPV) vaccine for at least 10 years; the Package Leaflet is updated accordingly. The RMP version 12.1 has also been submitted following revision 2. The MAH is taking the opportunity to implement minor editorial changes in the product information (SmPC, labelling and package leaflet)." Opinion adopted on 14.03.2019.	
IMVANEX - smallpox vaccine (live modified vaccinia virus ankara) - EMEA/H/C/002596/II/0035 Bavarian Nordic A/S, Rapporteur: Greg Markey, PRAC Rapporteur: Julie Williams, "Update of sections 4.4 and 4.8 of the SmPC in order to reflect the final results of study POX-MVA-037 (phase II, randomised, open-label, multicentre trial designed to evaluate the safety and immunogenicity of IMVANEX (MVA-BN smallpox vaccine) when increasing the dose or the number of injections compared with the standard 2-dose regimen in a population of adult, vaccinia naive, immunocompromised subjects with human immunodeficiency virus (HIV) infection), listed as a category 3 study in the RMP (described as post authorisation MEA 007); The RMP version 7.1 has also been submitted. Moreover, the PI is brought in line with the latest QRD template version 10." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 17.01.2019, 04.10.2018.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Kineret - anakinra - EMEA/H/C/000363/II/0064/G Swedish Orphan Biovitrum AB (publ), Rapporteur: Mark Ainsworth, PRAC Rapporteur: Anette Kirstine Stark, "Update of section 4.4 of the SmPC in order to add a warning on pulmonary events based on post-marketing data. The package leaflet is updated accordingly. Consequently, the important potential risks and the list of target medical events in the RMP (version 4.6) are updated to include pulmonary events and a specific follow-up questionnaire is created. The RMP is also revised in line with the GVP Module V RMP template (revision 2). In addition, the due date for submission of the final study report for the post-authorisation study (Sobi ANAKIN-302) is proposed to be extended. Furthermore, the MAH took the opportunity to	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

move the text about macrophage activation syndrome (MAS) and malignancies from section 4.8 to 4.4 of the SmPC." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 14.02.2019.	
Mimpara - cinacalcet - EMEA/H/C/000570/II/0062/G Amgen Europe B.V., Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, "Update to Section 4.4 of the SmPC to provide additional information on switching from etelcalcetide to Mimpara (cinacalcet), upon request by PRAC following the assessment of the etelcalcetide PSUR (dated 14 June 2018). Further, the term 'silica, dental type' has been replaced by 'Amorphous silicon dioxide' in SmPC section 6.1. An updated RMP version 9.0 was provided as part of the application in order to align the RMP with the GVP Module V (template Rev 2) with consequential reclassification of existing safety concerns." Request for Supplementary Information adopted on 14.03.2019, 29.11.2018.	Request for supplementary information adopted with a specific timetable.
NINLARO - ixazomib - EMEA/H/C/003844/II/0014/G, Orphan Takeda Pharma A/S, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Annika Folin, "Group of variations consisting of a type 2 variation to include submission of final report of progression free survival (PFS) in fulfilment of SOB004 and a type IB variation to request and extension of the due date of SOB003. Annex II is amended accordingly. Consequently the RMP is updated (version 4.0)."	See 9.1
Nucala - mepolizumab - EMEA/H/C/003860/II/0021 GlaxoSmithKline Trading Services Limited, Rapporteur: Peter Kiely, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on final results from Study 200363 Part B and two open label extension (OLE) studies (201312 and MEA115666) listed as category 3 studies in the RMP. These are interventional post-authorisation safety studies conducted to assess the long-term (52 weeks) safety and tolerability of	Request for supplementary information adopted with a specific timetable.

mepolizumab when administered subcutaneously to patients aged 6 to 11 years old with severe eosinophilic asthma (study 200363 Part B), to describe the long-term safety profile of mepolizumab (MEA115666), and to provide extended treatment to subjects from study MEA115661 and further describe long-term safety in these subjects (study 201312).
The RMP (version 5.0) has also been submitted to reflect the completion of the studies and to be aligned with GVP Module V, rev.2 template."
Request for Supplementary Information adopted on 14.03.2019.

OPDIVO - nivolumab -
EMEA/H/C/003985/II/0060/G

Bristol-Myers Squibb Pharma EEIG, Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information from studies CA209171 (A Phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous (Sq) cell non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of Stage IIIb/IV Sq NSCLC) and CA209172 (A Phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma progressing after prior treatment containing an anti-CTLA-4 monoclonal antibody). In addition the MAH take the occasion to update annex II to reflect already fulfilled requirement regarding biomarkers data (ANX 005.3, ANX 006, ANX 023, ANX 024, ANX 026 and ANX 027). The RMP has been updated accordingly (submitted version 13.4)."

Truberzi - eluxadoline -
EMEA/H/C/004098/II/0009/G

Allergan Pharmaceuticals International Ltd, Rapporteur: Martina Weise, PRAC Rapporteur: Adam Przybylkowski, "Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information based on results from PK study ELX-PK-01 listed as a category 3 study in the RMP; this is a Single-dose, Open-label, Pharmacokinetic study of eluxadoline in Healthy Subjects with normal Renal Function and Patients with Renal Impairment.

Update of sections 4.4 and 4.8 of the SmPC following Company Core Data Sheet (CCDS) update based on review of clinical safety data and post- marketing safety data. Section 4.3 has been updated to add clarification in line with section 4.4. and Section 5.1 has been updated to add Pharmacotherapeutic Group and ATC code. The RMP version 3.0 has also been submitted. The Package Leaflet is updated accordingly. In addition, the MAH also took the opportunity to change “eluxadoline” to “Truberzi” when referring to the medicinal product throughout the SmPC.”	
Wakix - pitolisant - EMEA/H/C/002616/II/0017, Orphan BIOPROJET PHARMA, Rapporteur: Joseph Emmerich, PRAC Rapporteur: Kirsti Villikka, “Update of sections 4.4, 4.5, 4.6 of the SmPC in order to reflect available information of co-administration of pitolisant with CYP3A4 substrats based on the results from studies R-B478-2.649, R.BF2.649-SK-005, R-B472-1.11413. The MAH took the opportunity to update the section 5.2 of SMPC to more accurately reflect information previously assessed during procedure EMEA/H/C/2616/II/0004/G (CD 13/10/2017). The RMP version 6.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to clarify the details about finished product manufacturers in the Package Leaflet.” Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
Xiapex - collagenase clostridium histolyticum - EMEA/H/C/002048/II/0107 Swedish Orphan Biovitrum AB (publ), Rapporteur: Janet Koenig, PRAC Rapporteur: Martin Huber, “Update of sections 4.4 and 5.1 of the SmPC to update the efficacy and safety information following the final results from study AUX-CC-810: Long-term Safety, Curvature Deformity, Characterization, and Immunogenicity over time in Subjects Previously Treated with AA4500 for Peyronie’s Disease in Studies AUX-CC-802, AUX-CC-803, AUC-X-CC-804, and AUX-CC-806; listed as a category 3 study in the RMP. The RMP version 14.1 has also been submitted. In addition, the Marketing authorisation holder	

took the opportunity to introduce minor editorial changes to SmPC and Package Leaflet."	
Xolair - omalizumab - EMEA/H/C/000606/II/0093 Novartis Europharm Limited, Rapporteur: Kristina Dunder, PRAC Rapporteur: Annika Folin, "Update of section 4.6 of the SmPC based on the data from the Xolair Pregnancy Registry (EXPECT) and final study report Q2952g listed as a category 3 study in the RMP; this is an observational study to evaluate pregnancy outcomes and estimate the incidence of spontaneous fetal loss in pregnant women exposed to omalizumab prenatally and to explore the potential risk to newborn infants exposed via breast milk. The Package Leaflet is proposed to be updated accordingly. The RMP version 14.0 has also been submitted." Request for Supplementary Information adopted on 13.12.2018.	
Xyrem - sodium oxybate - EMEA/H/C/000593/II/0078 UCB Pharma S.A., Rapporteur: Bruno Sepodes, PRAC Rapporteur: Ana Sofia Diniz Martins, "Submission of the final clinical study report (CSR) for the Post-Authorization Safety Study (PASS) NA0001 "Xyrem EU-RMP: Effectiveness Assessment of Educational Materials" ." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
Yervoy - ipilimumab - EMEA/H/C/002213/II/0064 Bristol-Myers Squibb Pharma EEIG, Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Menno van der Elst, "Update of section 4.8 of the SmPC in order to update the safety information following final results from study CA184143 (A Multi-National, Prospective, Observational Study in Patients with Unresectable or Metastatic Melanoma) listed as a category 3 study in the RMP (MEA017.11); The RMP has been updated accordingly (submitted version 26.0). In addition, the Marketing authorisation holder (MAH) took the opportunity to update the RMP in regards to already assessed MEA 036.1 concerning protocol synopsis on the extension of the Dutch Melanoma Treatment Registry (DMTR) to paediatric melanoma patients treated with ipilimumab. Furthermore the MAH took the	Request for supplementary information adopted with a specific timetable.

opportunity to request a 6-month shift in the dates associated to the next implementation steps of the DMTR extension (Registration of paediatric patients in the DMTR register and final CSR submission). Editorial changes have also been included in section 5.1 of the SmPC to provide more clarity on whether studies relate to melanoma or RCC and to monotherapy or combination therapy with nivolumab." Request for Supplementary Information adopted on 14.03.2019.	
Zejula - niraparib - EMEA/H/C/004249/II/0006, Orphan Tesaro Bio Netherlands B.V., Rapporteur: Bjorg Bolstad, PRAC Rapporteur: Jan Neuhauser, "Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to optimise the starting dose of niraparib and clarify dose modification information, modify the existing warning on haematologic adverse reactions, amend the description of thrombocytopenia and amend existing efficacy and pharmacokinetics information, respectively. The changes are based on the integrated Population clinical report that contains information from the completed Phase 3 NOVA, study submitted s part of the initial MAA, as well as supportive information from the ongoing phase 2 PR-30-5020-C (QUADRA) and phase 1 / 2 300-PN-162-01-001 (TOPACIO) studies. The update of the SmPC posology is based on exposure response study reports to propose alternative dosing strategies that aim to reduce Grade 3/4 thrombocytopenia; the Package Leaflet is updated accordingly. The RMP version 1.1 has also been submitted to reflect the new EU RMP format. Furthermore, the core sections of the RMP have been updated to: align with niraparib PSUR 1, reflect post-authorization experience, inclusion of embolic and thrombotic events as important potential risks and to optimize the starting dose of niraparib to reduce adverse events." Request for Supplementary Information adopted on 29.11.2018.	See 9.1
Zinforo - ceftaroline fosamil - EMEA/H/C/002252/II/0043 Pfizer Ireland Pharmaceuticals, Rapporteur: Alar Irs, PRAC Rapporteur: Maia Uusküla, "Update of section 4.2 of the SmPC in order to provide dosing recommendations for a high-dose	

regimen of ceftaroline fosamil in paediatric patients from 2 months to less than18 years of age for the treatment of complicated skin and soft tissue infections (cSSTI) for which Staphylococcus aureus is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L based on final study report of extrapolation study PMAR-EQDD-C266b-DP4-826. The RMP version 18.0 has also been submitted."	
WS1461 **Glyxambi-EMEA/H/C/003833/WS1461/0017** **Jentadueto-EMEA/H/C/002279/WS1461/0047** **Trajenta-EMEA/H/C/002110/WS1461/0035** Boehringer Ingelheim International GmbH, Lead Rapporteur: Johann Lodewijk Hillege, Lead PRAC Rapporteur: Menno van der Elst, "Update of sections 4.4 , 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis and bullous pemphigoid and the efficacy and safety information based on final results from study listed as a category 3 in the RMP "A multicenter, international, randomized, parallel group, double blind, placebo-controlled CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk (CARMELINA)". The RMP have also been updated accordingly for all products (Trajenta and Jentadueto version 12.1, Glyxambi version 4.1) and to be in accordance with the revision 2 of the RMP template." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 29.11.2018.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1557 **Exelon-EMEA/H/C/000169/WS1557/0120** **Prometax-EMEA/H/C/000255/WS1557/0121** Novartis Europharm Limited, Lead Rapporteur: Alexandre Moreau, Lead PRAC Rapporteur: Ghania Chamouni, "Submission of the final report of the Drug Utilization Study (CENA713D2409) aimed to assess the extent of inappropriate use of Exelon and Prometax. The DUS final report is fulfilling the post-authorisation measures Exelon MEA 034 and Prometax MEA 035."	Request for supplementary information adopted with a specific timetable.

Request for Supplementary Information adopted on 14.03.2019.	

B.5.4. PRAC assessed procedures

PRAC Led **Cayston - aztreonam - EMEA/H/C/000996/II/0075, Orphan** Gilead Sciences Ireland UC, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Liana Gross-Martirosyan, PRAC-CHMP liaison: Johann Lodewijk Hillege, "Submission of an updated RMP for Cayston in order to comply with Revision 2 of the EU-RMP template, in accordance with the revised guidance in the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011; Revision 2). RMP Version 8.0 is approved with this variation." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 17.01.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
PRAC Led **Fasenra - benralizumab - EMEA/H/C/004433/II/0017** AstraZeneca AB, Rapporteur: Fátima Ventura, PRAC Rapporteur: David Olsen, PRAC-CHMP liaison: Bjorg Bolstad, "Update of section 4.4 of the SmPC in order to add a warning on the risk of anaphylactic reactions and section 4.8 to add anaphylaxis as new adverse reaction with a frequency "not known" following the EMA Signal Assessment Report from PRAC (EPITT 19319) on cases of serious hypersensitivity including anaphylactic reaction. The package Leaflet is updated accordingly. The RMP is also updated in order to upgrade this risk to an important identified risk." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
PRAC Led **Gardasil - human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) - EMEA/H/C/000703/II/0081** MSD Vaccins, PRAC Rapporteur: Ulla Wändel Liminga, PRAC-CHMP liaison: Kristina Dunder, "Submission of an updated RMP version 13.1 in order to update the list of safety concerns by removing all remaining important identified and potential risks and missing information." Request for Supplementary Information adopted	Request for supplementary information adopted with a specific timetable.

on 14.03.2019.	
PRAC Led **Kengrexal - cangrelor - EMEA/H/C/003773/II/0015** Chiesi Farmaceutici S.p.A., Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Amelia Cupelli, PRAC-CHMP liaison: Daniela Melchiorri, "Submission of an updated RMP version 2.0 in order to update the requirements for a study listed as category 3 in the RMP. In addition, the MAH took the opportunity to revise the RMP in line with the RMP template version 2.0." Request for Supplementary Information adopted on 14.03.2019, 14.02.2019, 06.09.2018.	Request for supplementary information adopted with a specific timetable.
PRAC Led **Keytruda - pembrolizumab - EMEA/H/C/003820/II/0068** Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Menno van der Elst, PRAC-CHMP liaison: Johann Lodewijk Hillege, "C.I.11: Submission of an updated RMP version 23.1 in order to discuss the effectiveness of the educational materials put in place for Keytruda at the time of the initial marketing authorization and to provide a proposal to update these materials as well as to revise the safety specification as requested by PRAC during PSUSA/00010403/2018 procedure." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
PRAC Led **Neofordex - dexamethasone - EMEA/H/C/004071/II/0008** Laboratoires CTRS, Rapporteur: Greg Markey, PRAC Rapporteur: Ghania Chamouni, PRAC-CHMP liaison: Alexandre Moreau, "Submission of an updated RMP version 4.2 in order to delete the category 3 activity 'Development of a 20mg oral dosage form' and update the due date of the category 3 activity 'removal of the score line for subdivision of the 40mg tablet and consequent deletion of the 20mg posology'. In addition, the MAH implemented the RMP revision 2 format." Opinion adopted on 21.03.2019. Request for Supplementary Information adopted on 06.09.2018.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
PRAC Led **Neulasta - pegfilgrastim -**	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP

EMEA/H/C/000420/II/0099 Amgen Europe B.V., Rapporteur: Greg Markey, PRAC Rapporteur: Patrick Batty, PRAC-CHMP liaison: Greg Markey, "Submission of an updated RMP version 5.1 in order to add study 20160176, a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US SEER-Medicare database to estimate the risk of acute myeloid leukemia/myelodysplastic syndrome for breast cancer patients, as a new Pharmacovigilance activity (category 3). In addition the MAH submitted the draft protocol for study 20160176." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 29.11.2018, 12.07.2018.	Members were in agreement with the CHMP recommendation.
PRAC Led **Orencia - abatacept - EMEA/H/C/000701/II/0124/G** Bristol-Myers Squibb Pharma EEIG, Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Kimmo Jaakkola, PRAC-CHMP liaison: Outi Mäki-Ikola, "Submission of the final reports from studies IM101125, IM101127, IM101211, IM101213 and the interim report from study IM101121 listed as category 3 studies in the RMP. These are biologic registries and pharmacoepidemiology studies to assess the risk associated with the use of abatacept during post-marketing in geographically diverse populations and subgroups. Submission of the final study report from study IM101488 as supporting study but not listed in the RMP. This is a retrospective cohort study assessing the long-term safety of abatacept. The deadline for submission of the final study report from study IM101121 (pregnancy registry) is proposed to be extended. The RMP (version 26) is updated to reflect the completion of the studies IM101125, IM101127, IM101211, and IM101213, to update the information from studies IM101211 with the proposed extended deadline for submission of the final study report and to add two additional epidemiological studies IM101803 and IM101W52 as category 3 studies in the RMP. In addition, the MAH proposes to remove the following missing information items: combination therapy, including biologic therapy, and elderly	Request for supplementary information adopted with a specific timetable.

patients." Request for Supplementary Information adopted on 14.03.2019.	
PRAC Led **Otezla - apremilast -** **EMEA/H/C/003746/II/0023** Celgene Europe BV, Rapporteur: Peter Kiely, PRAC Rapporteur: Eva A. Segovia, PRAC-CHMP liaison: Concepcion Prieto Yerro, "Submission of an updated RMP version 11.0 in order to reclassify and/or rename the known safety concerns associated with the use of apremilast in accordance with the new Guideline on GVP Module V. In addition, the RMP is converted to the RMP template Revision 2." Request for Supplementary Information adopted on 14.03.2019, 31.10.2018.	Request for supplementary information adopted with a specific timetable.
PRAC Led **Somavert - pegvisomant -** **EMEA/H/C/000409/II/0089** Pfizer Europe MA EEIG, Rapporteur: Joseph Emmerich, PRAC Rapporteur: Adrien Inoubli, PRAC-CHMP liaison: Joseph Emmerich, "Submission of the final report from ACROSTUDY (Study A6291010), an open-label, global, non-interventional post-authorisation safety study (PASS) performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice. This final CSR relates to the Post Approval Measure MEA 059, listed as a category 3 study in the RMP." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
PRAC Led **Zaltrap - aflibercept -** **EMEA/H/C/002532/II/0051** sanofi-aventis groupe, Rapporteur: Filip Josephson, PRAC Rapporteur: Annika Folin, PRAC-CHMP liaison: Filip Josephson, "Submission of the final report from study OBS13597 / OZONE listed as a category 3 study in the RMP. This is a Prospective international observational cohort non-comparative study describing the safety and effectiveness of ZALTRAP administered in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer in current clinical practice: A Post-Authorisation Safety Study (PASS). The RMP is updated accordingly and also transposed to revision 2	Request for supplementary information adopted with a specific timetable.

including revision of the List of Safety Concerns according to GVP module V Rev 2." Request for Supplementary Information adopted on 14.03.2019.	
PRAC Led **Zydelig - idelalisib - EMEA/H/C/003843/II/0046** Gilead Sciences Ireland UC, Rapporteur: Filip Josephson, PRAC Rapporteur: Martin Huber, PRAC-CHMP liaison: Martina Weise, "Submission of the clinical study report for study GS-EU-313-4226, A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig in the European Union. This is a category 3 PASS study to assess the effectiveness of additional risk minimization measures by determining the level of knowledge of haematologists and oncologists (who manage patients with CLL or FL) about the infection risks associated with Zydelig treatment and the corresponding recommendation to minimize these risks as outlined in the SmPC and communicated in the direct healthcare professional communication (DHPC). This is to fulfill RMP post-authorisation measure MEA 016." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.
PRAC Led **WS1509** **Atripla-EMEA/H/C/000797/WS1509/0138** **Truvada-EMEA/H/C/000594/WS1509/0158** Gilead Sciences Ireland UC, Lead Rapporteur: Janet Koenig, Lead PRAC Rapporteur: Martin Huber, PRAC-CHMP liaison: Janet Koenig, "Submission of updated RMPs version 18.0 for Atripla and version 16.0 for Truvada, in order to: 1) implement Revision 2 of the EU-RMP template and amend the safety concerns accordingly, 2) remove the additional risk minimisation measures for tenofovir disoproxil fumarate in the form of education materials regarding renal toxicity and bone events, with the resulting amendment of Annex II of the product information, 3) add clinical data from study GS-US-104-0352 (A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate Versus Continuing	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy), 4) revise the due dates for two category 3 studies for Truvada, GS-US-276-0103 (A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada for Pre Exposure Prophylaxis (PrEP)) and GS-EU-276-4027 (A Cross-Sectional Post Authorization Safety Study to Assess Healthcare Provider's Level of Awareness of Risk Minimisation Materials for Truvada for Pre Exposure Prophylaxis in the European Union), 5) change the Marketing Authorisation Holder's (MAH) name from Gilead Sciences International Ltd. to Gilead Sciences Ireland UC., 6) update the milestones for the Truvada study GS-US-276-0104 (Seroconversions, Resistance, Adverse Events and Drug Adherence among Subjects taking Truvada for PrEP: A Nested Case Control study) in the Truvada EU-RMP and 7) correct a discrepancy in Annex IIIB of the Truvada PI regarding the recommendation pertaining to pregnancy, by aligning the PL wording with that of the SmPC." Opinion adopted on 14.03.2019. Request for Supplementary Information adopted on 17.01.2019.	
PRAC Led **WS1526** **Enbrel-EMEA/H/C/000262/WS1526/0223** **LIFMIOR-EMEA/H/C/004167/WS1526/0018** Pfizer Europe MA EEIG, Lead Rapporteur: Concepcion Prieto Yerro, Lead PRAC Rapporteur: Eva A. Segovia, PRAC-CHMP liaison: Concepcion Prieto Yerro, "Submission of the final report from study (RABBIT register Cohort 2) listed as a category 3 study in the RMP. This is a prospective, non-interventional, observational, long-term cohort Germanic biologics register to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) in comparison to cohorts of RA patients treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic (b)DMARDs." Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
PRAC Led **WS1536**	Request for supplementary information adopted with a specific timetable.

Levitra-EMEA/H/C/000475/WS1536/0064 **Vivanza-EMEA/H/C/000488/WS1536/0060** Bayer AG, Lead Rapporteur: Concepcion Prieto Yerro, Lead PRAC Rapporteur: Maria del Pilar Rayon, PRAC-CHMP liaison: Concepcion Prieto Yerro, "Submission of the final clinical study report of a non-interventional PASS (category 3 study) to investigate the NAION risk associated with PDE5 inhibitors together with a consequential update of the RMP." Request for Supplementary Information adopted on 14.03.2019.	
PRAC Led **WS1543** **Ultibro Breezhaler-EMEA/H/C/002679/WS1543/0029** **Ulunar Breezhaler-EMEA/H/C/003875/WS1543/0029** **Xoterna Breezhaler-EMEA/H/C/003755/WS1543/0033** Novartis Europharm Limited, Lead Rapporteur: Mark Ainsworth, Lead PRAC Rapporteur: Anette Kirstine Stark, PRAC-CHMP liaison: Sinan B. Sarac, "Submission of the final study report of the Category I Post-Authorisation Safety Study (PASS) CQVA149A2402 (Multinational database cohort study in Europe in COPD patients, to assess the incidence rates and hazard ratios of various safety outcomes in new users of indacaterol/glycopyrronium compared to new users of comparator drugs (at the drug-class level). The PI has been updated by the removal of the black triangle and amendments in Annex II.D (Conditions or restrictions with regard to the safe and effective use of the medicinal product). RMP version 5.0 has been submitted accordingly." Request for Supplementary Information adopted on 14.03.2019.	Request for supplementary information adopted with a specific timetable.

B.5.5. CHMP-CAT assessed procedures

YESCARTA - axicabtagene ciloleucel - EMEA/H/C/004480/II/0003, Orphan, ATMP Kite Pharma EU B.V., Rapporteur: Jan Mueller-Berghaus, CHMP Coordinator: Jan Mueller-Berghaus, "Update of the sections 4.8, 5.1 of the SmPC to add information based on	

Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1), an addendum presenting 24-month analysis. The Package Leaflet has been updated accordingly.
Furthermore, editorial changes have been introduced throughout the PI."
Request for Supplementary Information adopted on 25.01.2019.

B.5.6. CHMP-PRAC-CAT assessed procedures

Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0029, ATMP
Amgen Europe B.V., Rapporteur: Olli Tenhunen, CHMP Coordinator: Tuomo Lapveteläinen, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of section 5.2 of the SmPC in order to update the pharmacokinetic properties information based on the final results from study 20120324, a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. This submission fulfils MEA 006.1. In addition, the Marketing authorisation holder (MAH) took the opportunity to update Annex II as per the already assessed EMEA/H/C/002771/ANX/001 procedure.
In addition, the MAH took the opportunity to update the details of local representatives for Ireland and Portugal in the package leaflet."
Opinion adopted on 22.03.2019.
Request for Supplementary Information adopted on 22.02.2019.

B.5.7. PRAC assessed ATMP procedures

PRAC Led
Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0028, ATMP
Amgen Europe B.V., Rapporteur: Olli Tenhunen, CHMP Coordinator: Tuomo Lapveteläinen, PRAC Rapporteur: Brigitte Keller-Stanislawski, PRAC-CHMP liaison: Jan Mueller-Berghaus, "Submission of an updated RMP version 5.1 in order to align the important identified and potential risks and missing information with the revised guideline Good Pharmacovigilance Practices Module V (Revision 2), resulting in the

reclassification and removal of a number of identified and potential risks and missing information." Opinion adopted on 22.03.2019. Request for Supplementary Information adopted on 07.12.2018.	

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

WS1489/G **Suboxone-EMEA/H/C/000697/WS1489/0039/G** Indivior Europe Limited, Lead Rapporteur: Janet Koenig Request for Supplementary Information adopted on 24.01.2019.	
WS1494 **HyQvia-EMEA/H/C/002491/WS1494/0046** **Kiovig-EMEA/H/C/000628/WS1494/0087** Baxalta Innovations GmbH, Lead Rapporteur: Jan Mueller-Berghaus Opinion adopted on 07.03.2019. Request for Supplementary Information adopted on 31.01.2019.	Positive Opinion adopted by consensus on 07.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1529 **Ambirix-EMEA/H/C/000426/WS1529/0094** **Cervarix-EMEA/H/C/000721/WS1529/0100** **Infanrix hexa-EMEA/H/C/000296/WS1529/0255** **Rotarix-EMEA/H/C/000639/WS1529/0111** **Twinrix Adult-EMEA/H/C/000112/WS1529/0129** **Twinrix Paediatric-EMEA/H/C/000129/WS1529/0130** GlaxoSmithkline Biologicals SA, Lead Rapporteur: Bart Van der Schueren Opinion adopted on 21.03.2019.	Positive Opinion adopted by consensus on 21.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1531 **Herceptin-EMEA/H/C/000278/WS1531/0150** **Kadcyla-EMEA/H/C/002389/WS1531/0043** Roche Registration GmbH, Lead Rapporteur: Jan Mueller-Berghaus Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1560	Request for supplementary information adopted

Renvela-EMEA/H/C/000993/WS1560/0048 **Sevelamer carbonate Winthrop-EMEA/H/C/003971/WS1560/0019** Genzyme Europe BV, Lead Rapporteur: Bart Van der Schueren, “To introduce new presentation with new dosing spoon for Renvela (EU/1/09/521/009) and Sevelamer carbonate Winthrop (EU/1/14/952/006) 0.8 g powder for oral suspension sachet. This variation fulfils commitment to develop a suitable device which would allow the accurate administration of the minimum 0.4g increments of sevelamer carbonate, that was undertaken during the line extension procedures. In addition, the MAH took the opportunity to introduce editorial changes in the product information.” Request for Supplementary Information adopted on 14.03.2019.	with a specific timetable.
WS1561 **Enurev Breezhaler-EMEA/H/C/002691/WS1561/0029** **Seebri Breezhaler-EMEA/H/C/002430/WS1561/0029** **Tovanor Breezhaler-EMEA/H/C/002690/WS1561/0033** Novartis Europharm Limited, Lead Rapporteur: Mark Ainsworth Opinion adopted on 14.03.2019.	Positive Opinion adopted by consensus on 14.03.2019. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.
WS1562/G **Aflunov-EMEA/H/C/002094/WS1562/0047/G** **Foclivia-EMEA/H/C/001208/WS1562/0042/G** Seqirus S.r.l, Lead Rapporteur: Daniela Melchiorri	
WS1563/G **Glyxambi-EMEA/H/C/003833/WS1563/0018/G** **Jardiance-EMEA/H/C/002677/WS1563/0041/G** **Synjardy-EMEA/H/C/003770/WS1563/0037/G** Boehringer Ingelheim International GmbH, Lead Rapporteur: Johann Lodewijk Hillege	
WS1565 **Halimatoz-EMEA/H/C/004866/WS1565/0008**	

Hefiya-EMEA/H/C/004865/WS1565/0008 **Hyrimoz-EMEA/H/C/004320/WS1565/0008** Sandoz GmbH, Lead Rapporteur: Milena Stain, "To update the Annex II of the Product Information to reflect the change in RMP of the originator in order to update the list of safety concerns in relation to prior assessments and in line with GVP Module V in line with the same change for the originator. In addition and as a consequence of the RMP update, the is updated in relation to the additional minimisation measure of the Patient Reminder Card. Consequential minor changes to the SmPC and PL are also made. In addition the MAH has reintroduced all approved indication to the annexes of Hefiya as they had been removed in error."	
WS1570 **Ultibro Breezhaler-EMEA/H/C/002679/WS1570/0030** **Ulunar Breezhaler-EMEA/H/C/003875/WS1570/0030** **Xoterna Breezhaler-EMEA/H/C/003755/WS1570/0034** Novartis Europharm Limited, Lead Rapporteur: Mark Ainsworth	

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

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

Firdapse - amifampridine - EMEA/H/C/001032/II/0060, Orphan BioMarin International Limited, Rapporteur: Kristina Dunder, "Update section 5.1 of the SmPC to include results from study LMS-003: a double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of amifampridine in patients with Lambert-Eaton Myasthenic Syndrome (LEMS)." Request for Supplementary Information adopted on 17.01.2019.	Request for an extension to the clock stop to respond to the Request for Supplementary Information adopted on 17.01.2019. Adoption by written procedure on 14.03.2019.
Forsteo - teriparatide - EMEA/H/C/000425/II/0050/G Eli Lilly Nederland B.V., Rapporteur: Alexandre Moreau, PRAC Rapporteur: Adrien Inoubli, PRAC-CHMP liaison: Alexandre Moreau,	Request for an extension to the clock stop to respond to the Request for Supplementary Information adopted on 14.02.2019.

"Submission of the final study reports of the European Union (EU) components of two post-authorisation safety studies (PASS); Study B3DMC-GHBX(2.2) and Study B3D-MC-GHBX(2.3b) both US population-based comparative cohort studies undertaken to evaluate a potential association between teriparatide and adult Osteosarcoma. An updated RMP version 7.0 was submitted as part of the application." Request for Supplementary Information adopted on 14.02.2019.	
WS1502 **Fertavid-EMEA/H/C/001042/WS1502/0042** **Puregon-EMEA/H/C/000086/WS1502/0100** Merck Sharp & Dohme B.V., Lead Rapporteur: Nithyanandan Nagercoil Request for Supplementary Information adopted on 07.03.2019, 06.12.2018.	Request for an extension to the clock stop to respond to the Request for Supplementary Information adopted on 07.03.2019.

B.6. START OF THE PROCEDURES TIMETABLES FOR INFORMATION

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

darolutamide - EMEA/H/C/004790 treatment of non-metastatic castration resistant prostate cancer (nmCRPC)

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

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

autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - EMEA/H/C/003691, Orphan, ATMP bluebird bio GmbH, treatment of transfusion-dependent β-thalassaemia (TDT) List of Questions adopted on 25.01.2019.

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

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

Brimica Genuair - aclidinium / formoterol fumarate dihydrate - EMEA/H/C/003969/R/0026
AstraZeneca AB, Duplicate, Duplicate of Duaklir Genuair, Rapporteur: Ewa Balkowiec Iskra, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Adam Przybylkowski

Cyramza - ramucirumab - EMEA/H/C/002829/R/0031
Eli Lilly Nederland B.V., Rapporteur: Paula Boudewina van Hennik, Co-Rapporteur: Kolbeinn Gudmundsson (IS) (MNAT with IS for Clinical Efficacy, IS for Clinical Safety, IS for Coordination, FI for Quality, FI for Non-Clinical, LT for Clinical Pharmacology), PRAC Rapporteur: Brigitte Keller-Stanislawski

Duaklir Genuair - aclidinium / formoterol fumarate dihydrate - EMEA/H/C/003745/R/0026
AstraZeneca AB, Rapporteur: Ewa Balkowiec Iskra, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Adam Przybylkowski

Duloxetine Lilly - duloxetine - EMEA/H/C/004000/R/0015
Eli Lilly Nederland B.V., Rapporteur: Concepcion Prieto Yerro, Co-Rapporteur: Filip Josephson, PRAC Rapporteur: Maria del Pilar Rayon

Harvoni - ledipasvir / sofosbuvir - EMEA/H/C/003850/R/0080
Gilead Sciences Ireland UC, Rapporteur: Filip Josephson, Co-Rapporteur: Joseph Emmerich, PRAC Rapporteur: Ana Sofia Diniz Martins

Ketoconazole HRA - ketoconazole - EMEA/H/C/003906/R/0014, Orphan
Laboratoire HRA Pharma, Rapporteur: Concepcion Prieto Yerro, Co-Rapporteur: Peter Kiely, PRAC Rapporteur: Željana Margan Koletić

Lymphoseek - tilmanocept - EMEA/H/C/002085/R/0016
Norgine B.V., Rapporteur: Jayne Crowe, Co-Rapporteur: Peter Kiely, PRAC Rapporteur: Rugile Pilviniene

Moventig - naloxegol - EMEA/H/C/002810/R/0028
Kyowa Kirin Holdings B.V., Rapporteur: Bart Van

der Schueren, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Ronan Grimes

MULTAQ - dronedarone - EMEA/H/C/001043/R/0042
sanofi-aventis groupe, Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Agnes Gyurasics, PRAC Rapporteur: Menno van der Elst

OFEV - nintedanib - EMEA/H/C/003821/R/0025, Orphan
Boehringer Ingelheim International GmbH, Rapporteur: Jayne Crowe, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Nikica Mirošević Skvrce

Rezolsta - darunavir / cobicistat - EMEA/H/C/002819/R/0031
Janssen-Cilag International NV, Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Amelia Cupelli

Tadalafil Mylan - tadalafil - EMEA/H/C/003787/R/0014
Mylan S.A.S, Generic, Generic of Cialis, Rapporteur: Kolbeinn Gudmundsson, PRAC Rapporteur: Maria del Pilar Rayon

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

Bavencio - avelumab - EMEA/H/C/004338/II/0009/G, Orphan
Merck Europe B.V., Rapporteur: Filip Josephson, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Anette Kirstine Stark, “Extension of indication to include a new indication for Bavencio as the first-line combination treatment with avelumab and axitinib in adult patients with advanced renal cell carcinoma; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1. 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) takes the occasion to include change in posology section 4.2 of the SmPC to support the switch of the avelumab dosing regimen from 10 mg/kg every two weeks (weight-based) to a flat dose of 800 mg every two weeks applicable to the new proposed indication aRCC and the already

existing one (MCC). The MAH took the occasion to also implement some editorial changes in the Product information. A proposed updated RMP has been submitted as well in version 1.7”

Kadcyla - trastuzumab emtansine - EMEA/H/C/002389/II/0045

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Anette Kirstine Stark, “Extension of indication to include the adjuvant treatment of adult patients with HER2-positive early breast cancer, as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Applicant took the opportunity to introduce editorial changes.” Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Keytruda - pembrolizumab - EMEA/H/C/003820/II/0072

Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Menno van der Elst, “Extension of indication to include a new indication for Keytruda; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to include editorial corrections to the updated version of the RMP (Version 25.1) submitted with this application.”

MabThera - rituximab - EMEA/H/C/000165/II/0162

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, Co-Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Anette Kirstine Stark, “Extension of indication to include the treatment of paediatric patients (aged ≥ 2 to <18 years old) with active polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA), for MA numbers EU/1/98/067/001-002 for MabThera; following efficacy and safety data from Clinical study report (CSR) WA25615 (also known as Paediatric Polyangiitis and Rituximab Study [PePRS]) which was conducted to fulfil the measure of the Paediatric Investigational Plan (PIP: EMEA-000308-PIP02-11-M01) agreed upon in the context of rituximab development for

treatment of adult patients with GPA and MPA (RAVE study). The CSR for Study 1: WA 25615 was submitted on 30th Oct 2018 as the Post Approval Measure submission according to Article 46 requirement. Linked to this variation the final compliance check procedure to close the PIP has started 3rd January 2019.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 2, 3 and 4 of the Package Leaflet are updated accordingly.
Furthermore, the PI is brought in line with the latest QRD template (version 10) and the opportunity is taken to combine the SmPC and PIL for 100mg and 500mg IV as they are identical except for strength specifications.
In addition, the applicant took the opportunity to implement minor editorial changes in the SmPC.
The RMP version 20.0 has also been submitted."

Revlimid - lenalidomide - EMEA/H/C/000717/II/0107, Orphan
Celgene Europe BV, Rapporteur: Alexandre Moreau, Co-Rapporteur: Filip Josephson, PRAC Rapporteur: Ghania Chamouni, "Extension of indication to include Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; the PL is updated in accordance. An updated EU RMP (version 36.2) has also been submitted."

B.6.8. CHMP assessed procedures scope: Pharmaceutical aspects

Benepali - etanercept - EMEA/H/C/004007/II/0042/G
Samsung Bioepis NL B.V., Rapporteur: Andrea Laslop

Busilvex - busulfan - EMEA/H/C/000472/II/0030/G
Pierre Fabre Medicament, Rapporteur: Jorge Camarero Jiménez

Evicel - human fibrinogen / human thrombin - EMEA/H/C/000898/II/0067
Omrix Biopharmaceuticals N. V., Rapporteur: Jan Mueller-Berghaus

Flucelvax Tetra - influenza vaccine surface antigen inactivated prepared in cell cultures

- EMEA/H/C/004814/II/0004/G
Seqirus Netherlands B.V., Rapporteur: Sol Ruiz

Insuman - insulin human - EMEA/H/C/000201/II/0128/G
Sanofi-Aventis Deutschland GmbH, Rapporteur: Bart Van der Schueren

Macimorelin Aeterna Zentaris - macimorelin - EMEA/H/C/004660/II/0001
Aeterna Zentaris GmbH, Rapporteur: Martina Weise

Movymia - teriparatide - EMEA/H/C/004368/II/0012
STADA Arzneimittel AG, Duplicate, Duplicate of Terrosa, Rapporteur: Milena Stain

Myalepta - metreleptin - EMEA/H/C/004218/II/0004, Orphan
Aegerion Pharmaceuticals B.V., Rapporteur: Bart Van der Schueren

Ogivri - trastuzumab - EMEA/H/C/004916/II/0003/G
MYLAN S.A.S, Rapporteur: Koenraad Norga

Prasugrel Mylan - prasugrel - EMEA/H/C/004644/II/0003/G
Mylan S.A.S, Generic, Generic of Efient, Rapporteur: Alar Irs

Respreeza - human alpha1-proteinase inhibitor - EMEA/H/C/002739/II/0029/G
CSL Behring GmbH, Rapporteur: Kristina Dunder

Terrosa - teriparatide - EMEA/H/C/003916/II/0010
Gedeon Richter Plc., Rapporteur: Milena Stain

WS1567
Ambirix-EMEA/H/C/000426/WS1567/0097
Twinrix Adult-EMEA/H/C/000112/WS1567/0132
Twinrix Paediatric-EMEA/H/C/000129/WS1567/0133
GlaxoSmithkline Biologicals SA, Lead Rapporteur: Bart Van der Schueren

WS1600/G
Aflunov-EMEA/H/C/002094/WS1600/0049/G
Foclivia-EMEA/H/C/001208/WS1600/0044/G

Seqirus S.r.l, Lead Rapporteur: Daniela Melchiorri

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

Bosulif - bosutinib - EMEA/H/C/002373/II/0037

Pfizer Europe MA EEIG, Rapporteur: Janet Koenig, PRAC Rapporteur: Martin Huber, "Update of sections 4.6 and 5.3 of the SmPC based on final results from study 17GR319 (00655202) rat pre-and post-natal development study (PPND) listed as a category 3 study in the RMP. The Package leaflet is updated accordingly. The updated RMP version 4.5 has also been submitted."

Increlex - mecasermin - EMEA/H/C/000704/II/0059

Ipsen Pharma, Rapporteur: Outi Mäki-Ikola, "Submission of the final analysis for the Category 3, Additional Pharmacovigilance Activity MEA 020.3, on Lowest Effective Dose for mecasermin. No changes to the SmPC or Patient Leaflet are proposed as part of this final analysis on Lowest Effective Dose of mecasermin."

Keytruda - pembrolizumab - EMEA/H/C/003820/II/0071

Merck Sharp & Dohme B.V., Rapporteur: Daniela Melchiorri, "To update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study KEYNOTE-051; this is an ongoing Phase I/II, single-arm study to evaluate the PK, pharmacodynamics, toxicity, safety, and anti-tumour activity of pembrolizumab in paediatric participants (Measure 2 of PIP01). Additionally, the results of study Study PD018 / PA-0064; evaluation of expression of PD-1, PD-L1, and PD-L2 in archival paediatric tumour tissues, were submitted (Measure 1 of PIP01)."

Kovaltry - octocog alfa - EMEA/H/C/003825/II/0022

Bayer AG, Rapporteur: Kristina Dunder, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of the RMP version 2.0 in line with the GVP revision 2 and the new RMP template."

Lynparza - olaparib - EMEA/H/C/003726/II/0028

AstraZeneca AB, Rapporteur: Alexandre Moreau,

"Update of section 5.2 of the SmPC in order to include information on the in vitro effect of olaparib on UGT enzymes based on results from in vitro assays. In addition, the MAH is proposing to change the due date for submission of the final CSR of the phase IV, open label, single arm study (D0816C00012/ORZORA) in patients with relapsed platinum sensitive ovarian cancer who are in response following platinum-based chemotherapy, and who carry loss of function germline or somatic BRCA mutations listed as a PAES in the Annex II."	
Privigen - human normal immunoglobulin - EMEA/H/C/000831/II/0146 CSL Behring GmbH, Rapporteur: Jan Mueller-Berghaus, "Update of section 4.8 of the SmPC in order to add decreased neutrophil count to the list of adverse reactions with the frequency unknown. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to sections 4.2, 4.4, 4.8 and 5.1 of the SmPC and to the Package Leaflet."	
Privigen - human normal immunoglobulin - EMEA/H/C/000831/II/0147 CSL Behring GmbH, Rapporteur: Jan Mueller-Berghaus, "Update of section 2 of the SmPC in order to update the IgG subclass values according to performed analyses. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Bulgaria in the Package Leaflet."	
Spinraza - nusinersen - EMEA/H/C/004312/II/0013/G, Orphan Biogen Netherlands B.V., Rapporteur: Bruno Sepodes, "C1.3.b (Type II): to update sections 4.8 and 5.1 of the SmPC following assessment of the final CSR for Study CS3A (Procedure number: EMA/H/C/4312/P46/007). Study CS3A was a phase 2 open-label multiple dose study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of nusinersen (ISIS 396443) Delivered Intrathecally to Patients with Infantile-Onset Spinal Muscular Atrophy. 3xC.I.4 (Type II): to update sections 4.8 and 5.1 of the SmPC to reflect safety, efficacy, and	

immunogenicity data from the interim analyses of studies SM201 and CS11, and results of SM202, Part 1.
SM202 (EMBRACE) is a 2-part Phase 2 study in subjects with infantile- and later-onset SMA not eligible to participate in Studies CS3B or CS4.
CS11 (SHINE) is an on-going open label extension Phase 3 study for subjects with infantile and later onset SMA who previously participated in investigational studies of nusinersen, including Studies CS3A, CS12, CS3B, and CS4 and SM202.
SM201 (NURTURE) is an on-going multicentre, Phase 2, open label study in infants with genetically diagnosed, presymptomatic SMA."

Tecentriq - atezolizumab - EMEA/H/C/004143/II/0023

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, "Update of section 4.8 of the SmPC in order to include new ADRs identified in IMmotion150 and IMmotion151 studies. The revision of the list of ADRs is supported by a drug safety report reflecting the ADRs in the updated pool of patients for monotherapy (n=3178) and combination therapy (n=1345).
The Package Leaflet is updated accordingly."

Xarelto - rivaroxaban - EMEA/H/C/000944/II/0064

Bayer AG, Rapporteur: Kristina Dunder, "Submission of the final report from an interventional phase III study (COMMANDER HF, 2.5 mg rivaroxaban compared to placebo)."

WS1566
Biktarvy-EMEA/H/C/004449/WS1566/0017
Descovy-EMEA/H/C/004094/WS1566/0041
Genvoya-EMEA/H/C/004042/WS1566/0061
Odefsey-EMEA/H/C/004156/WS1566/0041
Vemlidy-EMEA/H/C/004169/WS1566/0019

Gilead Sciences Ireland UC, Lead Rapporteur: Bruno Sepodes, "Update of section 4.8 of the SmPC following a safety review by the MAH assessing the clinical evidence of a causal association between tenofovir alafenamide-containing products and two

adverse events, angioedema and urticaria. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic amendments and editorial changes to the product information."

WS1605
Lyrica-EMEA/H/C/000546/WS1605/0097
Pregabalin Pfizer-EMEA/H/C/003880/WS1605/0027
Pfizer Europe MA EEIG, Lead Rapporteur: Johann Lodewijk Hillege, "Addition in the SmPC section 4.5 of the wording on the risk of death, including in patients who are substance abusers."

WS1607
Kisplyx-EMEA/H/C/004224/WS1607/0023
Lenvima-EMEA/H/C/003727/WS1607/0025
Eisai GmbH, Lead Rapporteur: Bart Van der Schueren, "Update of section 5.2 of the SmPC in order to include information about the results of Study E7080-A001- 010, "A Multicenter Phase 0 Study in Healthy Subjects and Subjects with Either Hepatic or Renal Impairment to Obtain Plasma for Assessment in Vitro Lenvatinib Protein Binding"."

B.6.10. CHMP-PRAC assessed procedures

Jakavi - ruxolitinib -
EMEA/H/C/002464/II/0040
Novartis Europharm Limited, Rapporteur: Filip Josephson, PRAC Rapporteur: Annika Folin, "Update of section 5.3 of the SmPC in order to update the preclinical safety information based on final) results from studies from the juvenile toxicity studies 1570143 (dose range finding juvenile study) and 157014 (juvenile development study). These two studies are supporting the same SmPC.
Submission of an updated RMP version 10 in order to update the information accordingly. Furthermore, the RMP template and to the GVP Module V Rev.2 (EMA/838713/2011 Rev 2)."

Jakavi - ruxolitinib -
EMEA/H/C/002464/II/0041
Novartis Europharm Limited, Rapporteur: Filip Josephson, PRAC Rapporteur: Annika Folin, "to present the final results of a Drug-Drug Interaction (DDI) study (INC4242A2106),

fulfilling a Post-Authorisation Measure (MEA 0016) as part of a previous type II variation (Procedure No. EMEA/H/C/002464/II/0025). The study INC4242A2106 evaluated the effect of multiple doses of fluconazole on the pharmacokinetics of ruxolitinib administered as a single dose in an open-label, crossover study in healthy subjects. Submission of an updated RMP version 10 in order to update the information accordingly. Furthermore, the RMP template and to the GVP Module V Rev.2 (EMA/838713/2011 Rev 2)."	
WS1582 **Actraphane-EMEA/H/C/000427/WS1582/0076** **Actrapid-EMEA/H/C/000424/WS1582/0070** **Insulatard-EMEA/H/C/000441/WS1582/0073** **Mixtard-EMEA/H/C/000428/WS1582/0077** **Protaphane-EMEA/H/C/000442/WS1582/0072** Novo Nordisk A/S, Lead Rapporteur: Sinan B. Sarac, Lead PRAC Rapporteur: Anette Kirstine Stark, "To update the Human Insulin RMP to version 3.0 in order to reclassify the risk of 'Medication errors' (including human error-related medication errors) from an important potential risk to an important identified risk following a Pharmacovigilance Risk Assessment Committee (PRAC) request (EMEA/H/C/PSUSA/00001753/201710) and in accordance with the Good practice guide on risk minimisation and prevention of medication errors, issued by the PRAC in 2015. Furthermore, in accordance with the updated GVP Module V guidance on RMPs, the Worksharing Applicant (WSA) proposed to remove this risk as it is fully characterised and managed through routine pharmacovigilance and no additional pharmacovigilance activities or additional risk minimisation measures are planned or being currently undertaken. Information regarding the avoidance of accidental mix-ups/medication errors is included in the PIL for the concerned products. In consequence, section 4.4 of the SmPC was updated in order to add a warning on accidental mix-ups/medication.	

Additionally, the WSA took the opportunity include minor updates to Annex IIIA to bring the PI in line with the latest QRD template version."

B.6.11. PRAC assessed procedures

PRAC Led

Bydureon - exenatide - EMEA/H/C/002020/II/0059

AstraZeneca AB, Rapporteur: Kristina Dunder, PRAC Rapporteur: Annika Folin, PRAC-CHMP liaison: Kristina Dunder, "Submission of the final CSR for Study H80-MC-B016; a modified Prescription-Event Monitoring Program (Modified PEM) to be conducted in the UK, enrolling patients with Type 2 diabetes mellitus, to quantify the incidence of acute pancreatitis in the first 12 months after initiating treatment with prescription exenatide once weekly. An updated RMP version 33 was provided as part of the application. The provision of the final CSR addresses Post-authorisation Measure MEA 010.5."

PRAC Led

Darzalex - daratumumab - EMEA/H/C/004077/II/0027, Orphan

Janssen-Cilag International NV, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva, PRAC-CHMP liaison: Bruno Sepodes, "Update of sections 4.4. and 4.8 of the SmPC to add new safety information on the recently identified risk of Hepatitis B reactivation (HBV). Consequently the PIL is proposed to be updated. A revision of the RMP (v. 5) is included in the submission. The MAH also proposes a DHPC to inform prescribers on the newly identified risk."

PRAC Led

Neuraceq - florbetaben (18F) - EMEA/H/C/002553/II/0028

Life Radiopharma Berlin GmbH, Rapporteur: Concepcion Prieto Yerro, PRAC Rapporteur: Martin Huber, PRAC-CHMP liaison: Martina Weise, "Submission of the final report from non-interventional PASS study FBB-01_02_13 listed as a category 3 study in the RMP. This is a prospective observational study to assess effectiveness of the training and risk minimisation measures recommended for the

usage of the diagnostic agent NeuraCeq in the post-authorisation clinical situation.
The RMP version 3.9 has also been submitted."

PRAC Led

ProQuad - measles, mumps, rubella and varicella vaccine (live) - EMEA/H/C/000622/II/0134

MSD Vaccins, Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Brigitte Keller-Stanislawski, PRAC-CHMP liaison: Jan Mueller-Berghaus,
"Submission of an updated RMP (version 6.1) in order to adhere to Version 2 of the RMP template. As a consequence, the following changes are carried out:
- Removal of the important identified risks febrile seizure, fever, measles-like rash, and thrombocytopenia and the addition of disseminated disease caused by Oka/Merck vaccine virus strain.
- The important potential risks varicella-like or herpes zoster-like rashes, potential central nervous system events, potential transmission of varicella vaccine virus strain, exposure of immunocompromised individuals, hypersensitivity including anaphylaxis and injection-site reactions are also removed.
- Additionally, secondary transmission of Oka/Merck vaccine virus strain in susceptible high-risk individuals leading to severe clinical consequences is included.
- The important missing information 'categories exposure during pregnancy' and 'safety and immunogenicity in patients less than 9 months' of age is also removed."

PRAC Led

Vectibix - panitumumab - EMEA/H/C/000741/II/0093

Amgen Europe B.V., Rapporteur: Bjorg Bolstad, PRAC Rapporteur: David Olsen, PRAC-CHMP liaison: Bjorg Bolstad

PRAC Led

Votrient - pazopanib - EMEA/H/C/001141/II/0054

Novartis Europharm Limited, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Anette Kirstine Stark, PRAC-CHMP liaison: Sinan B. Sarac,
"Submission of an updated RMP version 17.0 in order to postpone CSR submission for "COMPARZ" study and its substudy, to reflect

PRAC recommendations for additional assessments of some risks, to revise the list of safety concerns, and to adapt to GVP template."

PRAC Led

WS1581

Rasilez-EMEA/H/C/000780/WS1581/0123

Rasilez HCT-EMEA/H/C/000964/WS1581/0093

Noden Pharma DAC, Lead Rapporteur: Daniela Melchiorri, Lead PRAC Rapporteur: Amelia Cupelli, PRAC-CHMP liaison: Daniela Melchiorri, "Submission of an updated RMP version 14 in order to update the template in line with GVP Module V Rev2 required, add new important potential risk of non-melanoma skin cancer (related to Rasilez HCT only), and remove several important risks and missing information items as per PRAC endorsement of PSUR 12."

PRAC Led

WS1586

Anoro Ellipta-EMEA/H/C/002751/WS1586/0028

Laventair Ellipta-EMEA/H/C/003754/WS1586/0031

GlaxoSmithKline (Ireland) Limited, Lead Rapporteur: Jayne Crowe, Lead PRAC Rapporteur: Amelia Cupelli, PRAC-CHMP liaison: Daniela Melchiorri, "Submission of an updated RMP version 8.0 following Annual Renewal Procedure (EMEA/H/C/4002751/R/0022/ EMEA/H/C/003754/R/0025) commitments to remove the important identified risks of Hypersensitivity and Paradoxical bronchospasm (which may be life-threatening) from the list of safety concerns and to update all relevant sections of the RMP accordingly.
MAH is also proposing to remove some additional risks (narrow angle glaucoma, Bladder outflow obstruction and urinary retention, Safety in pregnancy and lactation, Safety in long-term use, Safety in severe hepatic impairment), which have not been previously discussed with EMA."

PRAC Led

WS1596

Humalog-EMEA/H/C/000088/WS1596/0172

Liprolog-EMEA/H/C/000393/WS1596/0133

Eli Lilly Nederland B.V., Lead Rapporteur: Kristina

Dunder, Lead PRAC Rapporteur: Annika Folin, "Submission of the final report from on-going review of adverse drug events related to Humalog MEA/028 and Liprolog MEA/021, listed as a category 3 study in the RMP. This is a post approval safety surveillance programme for lot-specific adverse event review to evaluate any potential change in frequency of hypersensitivity, immunogenicity, and lack of drug effect (LODE) events for insulin lispro synthesized via streamlined KPB (sKPB) process."

PRAC Led
WS1603
Pregabalin Mylan-EMEA/H/C/004078/WS1603/0013
Pregabalin Mylan Pharma-EMEA/H/C/003962/WS1603/0011
Mylan S.A.S, Generic, Generic of Lyrica, Lead PRAC Rapporteur: Liana Gross-Martirosyan, PRAC-CHMP liaison: Johann Lodewijk Hillege, "To align the RMP with the originator (updated as part of procedure EMEA/H/C/000546/WS1364/0092). In addition the RMP is updated to the latest template and is also harmonised for all pregabalin marketing authorisations procedures for which Mylan has an approved RMP."

B.6.12. CHMP-CAT assessed procedures

B.6.13. CHMP-PRAC-CAT assessed procedures

B.6.14. PRAC assessed ATMP procedures

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

WS1572
Juluca-EMEA/H/C/004427/WS1572/0014
Tivicay-EMEA/H/C/002753/WS1572/0049
ViiV Healthcare B.V., Lead Rapporteur: Janet Koenig

WS1576/G
Blitzima-EMEA/H/C/004723/WS1576/0021/G
Ritemvia-EMEA/H/C/004725/WS1576/0021/G

Rituzena-EMEA/H/C/004724/WS1576/0022/G
Truxima-EMEA/H/C/004112/WS1576/0023/G
Celltrion Healthcare Hungary Kft., Lead Rapporteur: Sol Ruiz

WS1583
M-M-RVAXPRO-EMEA/H/C/000604/WS1583/0094
ProQuad-EMEA/H/C/000622/WS1583/0133
MSD Vaccins, Lead Rapporteur: Jan Mueller-Berghaus

WS1590
Segluromet-EMEA/H/C/004314/WS1590/0006
Steglatro-EMEA/H/C/004315/WS1590/0006
Steglujan-EMEA/H/C/004313/WS1590/0008
Merck Sharp & Dohme B.V., Lead Rapporteur: Kristina Dunder, “To update sections 4.4 and 4.8 of the SmPC in order to implement the PRAC Recommendation on the signal of Fournier's gangrene for SGLT-2 inhibitors. The Package leaflet is being updated accordingly.
In addition, the MAH is proposing an additional text the package leaflet to include the frequency of Fournier's gangrene, in alignment with the SmPC.”

WS1604
Filgrastim
Hexal-EMEA/H/C/000918/WS1604/0048
Zarzio-EMEA/H/C/000917/WS1604/0049
Hexal AG, Duplicate, Duplicate of Zarzio, Lead Rapporteur: Johann Lodewijk Hillege

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.

E.1. PMF Certification Dossiers:

E.1.1. Annual Update

E.1.2. Variations:

E.1.3. Initial PMF Certification:

E.2. Time Tables – starting & ongoing procedures: For information

PMF timetables starting and ongoing procedures	Tabled in MMD and sent by post mail (folder E).

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

G.1. Final Scientific Advice (Reports and Scientific Advice letters):

Information related to Scientific Advice cannot be released at the present time as these contain commercially confidential information.

G.2. Ongoing procedures

G.3. PRIME

Some information related to PRIME cannot be released at the present time as these contain commercially confidential information.

G.3.1. List of procedures concluding at 25-28 March 2019 CHMP plenary:

G.3.2. List of procedures starting in March 2019 for April 2019 CHMP adoption of outcomes

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