22 June 2015
EMA/CHMP/412522/2015
Procedure Management and Business Support Division

Committee for medicinal products for human use (CHMP)

Draft agenda for the meeting on 22-25 June 2015

Chair: Tomas Salmonson – Vice-Chair: Pierre Demolis

22 June 2015, 13:00 – 19:30, room 2A

23 June 2015, 08:30 – 19:30, room 2A

24 June 2015, 08:30 – 19:30, room 2A

25 June 2015, 08:30 – 16:00, room 2A

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 22-25 June 2015. See (current) June 2015 CHMP minutes (to be published post July 2015 CHMP meeting).

1.2. Adoption of agenda

CHMP agenda for 22-25 June 2015

1.3. Adoption of the minutes

CHMP minutes for 18-21 May 2015.

2. Oral Explanations

2.1. Pre-authorisation procedure oral explanations

2.1.1. - guanfacine - EMEA/H/C/003759

treatment of ADHD

Scope: Oral explanation

Action: Oral explanation to be held on Tuesday 23 June 2015 at **10.00**

List of Outstanding Issues adopted on 26.03.2015. List of Questions adopted on 24.07.2014.

Report from SAG Psychiatry meeting held on 1 June 2015.

2.1.2. - human alpha1-proteinase inhibitor - EMEA/H/C/002739

treatment of lung disease

Scope: Oral explanation

Action: Oral explanation to be held on Wednesday 24 June 2015 at 9.00.

List of Outstanding Issues adopted on 23.04.2015, 26.03.2015, 20.11.2014. List of Questions adopted on 25.04.2014.

2.1.3. - human heterologous liver cells - Orphan - ATMP - EMEA/H/C/003750

Cytonet GmbH&Co KG; treatment of urea cycle disorders (UCD)

Scope: Oral explanation to be held on Tuesday 23 June 2015 at 16.00.

Action: For adoption

List of Outstanding Issues adopted on 26.03.2015, 18.12.2014. List of Questions adopted on 25.04.2014.

2.1.4. - sebelipase alfa - Orphan - EMEA/H/C/004004

Synageva BioPharma Ltd; treatment of enzyme replacement therapy (ERT)

Scope: Possible oral explanation to be held on Wednesday 24 June 2015 at 11.00

Action: For adoption

List of Questions adopted on 23.04.2015.

BWP Report

See 3.1.5

2.2. Re-examination procedure oral explanations

2.3. Post-authorisation procedure oral explanations

2.4. Referral procedure oral explanations

2.4.1. Adrenaline auto injectors (EMEA/H/A-31/1398)

Rapporteur: Alar Irs, Co-Rapporteur: Robert James Hemmings,

Scope: Opinion or possible oral explanation by ALK-Abelló A/S on Wednesday 24 June 2015

Article 31 triggered by the MHRA due to the lack of robust evidence that the devices deliver the adrenaline intramuscularly in all patients.

Action: For adoption

List of Outstanding Issues adopted on 26.02.2015 and 25.09.2014. Ad-hoc expert group meeting held on 23 January 2015.

See 10.5.1

3. Initial applications

3.1. Initial applications; Opinions

3.1.1. - aripiprazole - EMEA/H/C/004008

treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 26.03.2015. List of Questions adopted on 20.11.2014.

3.1.2. - docetaxel - EMEA/H/C/003925

treatment of breast cancer, non-small cell lung cancer, prostate cancer, metastatic gastric adenocarcinoma and head and neck cancer

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 21.05.2015, 26.03.2015. List of Questions adopted on 23.10.2014.

3.1.3. - duloxetine - EMEA/H/C/003935

treatment depressive disorder, diabetic neuropathic pain, anxiety disorder, treatment depressive disorder, diabetic neuropathic pain, anxiety disorder

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 23.04.2015. List of Questions adopted on 22.01.2015.

3.1.4. - panobinostat - Orphan - EMEA/H/C/003725

Novartis Europharm Ltd; treatment of multiple myeloma

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 26.03.2015. List of Questions adopted on 25.09.2014.

3.1.5. - sebelipase alfa - Orphan - EMEA/H/C/004004

Synageva BioPharma Ltd; treatment of enzyme replacement therapy (ERT)

Scope: Possible Oral explanation / Opinion, BWP Report

Action: For adoption

See also 2.1.4

List of Questions adopted on 23.04.2015.

3.1.6. - sonidegib - EMEA/H/C/002839

treatment of basal cell carcinoma (BCC)

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 23.04.2015. List of Questions adopted on 25.09.2014.

3.1.7. - pregabalin - EMEA/H/C/004024

treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD),

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 21.05.2015. List of Questions adopted on 18.12.2014.

3.1.8. - idebenone - Orphan - EMEA/H/C/003834

Santhera Pharmaceuticals (Deutschland) GmbH; treatment of Leber's Hereditary Optic Neuropathy (LHON)

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 21.05.2015, 26.02.2015. List of Questions adopted on 25.09.2014.

3.1.9. - human alpha1-proteinase inhibitor - EMEA/H/C/002739

treatment of lung disease

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 23.04.2015, 26.03.2015, 20.11.2014. List of Questions adopted on 25.04.2014.

See 2.1.2

3.1.10. - asfotase alfa - Orphan - EMEA/H/C/003794

Alexion Europe SAS; treatment of paediatric-onset hypophosphatasia

Scope: Opinion

Action: For adoption

List of Outstanding Issues adopted on 21.05.2015, 26.03.2015. List of Questions adopted on 20.11.2014.

3.2. Initial applications; Day 180 list of outstanding issues

3.2.1. - cobimetinib - EMEA/H/C/003960

treatment of metastatic melanoma

Scope: Day 180 list of outstanding issue

Action: For adoption

List of Questions adopted on 22.01.2015.

3.2.2. - mercaptamine - Orphan - EMEA/H/C/003769

Orphan Europe S.A.R.L.; treatment of cystinosis

Scope: Day 180 list of outstanding issue

Action: For adoption

List of Questions adopted on 22.01.2015.

3.2.3. - talimogene laherparepvec – ATMP - EMEA/H/C/002771

treatment of adults with melanoma that is regionally or distantly metastatic

Scope: Day 180 list of outstanding issues, BWP Report

Action: For adoption

BWP Report

3.2.4. - pemetrexed - EMEA/H/C/004011

in combination with cisplatin is indicated for the treatment malignant pleural mesothelioma and non-small cell lung cancer

Scope: Day 180 list of outstanding issue

Action: For adoption

List of Questions adopted on 26.02.2015.

3.2.5. - glycerol phenylbutyrate - Orphan - EMEA/H/C/003822

Horizon Therapeutics Limited; treatment of patients with urea cycle disorders

Scope: Day 180 list of outstanding issue

Action: For adoption

List of Questions adopted on 23.10.2014.

3.2.6. - insulin human - EMEA/H/C/003858

treatment of diabetes

Scope: Day 180 list of outstanding issue

Action: For adoption

List of Questions adopted on 23.10.2014.

BWP Report

3.3. Initial applications; Day 120 list of questions

3.3.1. - amlodipine / valsartan - EMEA/H/C/004037

treatment of essential hypertension

Scope: Day 120 list of questions

Action: For adoption

3.3.2. - amikacin - Orphan - EMEA/H/C/003936

Insmed Limited; treatment of Pseudomonas aeruginosa lung infection/colonisation in cystic fibrosis patients, treatment of nontuberculous mycobacterial lung infection

Scope: Day 120 list of questions and revised timetable on similarity assessment

Action: For adoption

3.3.3. - pancreas powder - EMEA/H/C/002070

treatment in exocrine pancreatic insufficiency

Scope: Day 120 list of questions, BWP Report

Action: For adoption

3.3.4. BWP Report - carfilzomib - Orphan - EMEA/H/C/003790

Amgen Europe B.V.; treatment of multiple myeloma

Scope: Day 120 list of questions

Action: For adoption

3.3.5. - sirolimus - Orphan - EMEA/H/C/003978

Santen Oy; treatment of chronic non-infectious uveitis

Scope: Day 120 list of questions

Action: For adoption

3.3.6. - pemetrexed - EMEA/H/C/004109

treatment of malignant pleural mesothelioma and non-small cell lung cancer.

Scope: Day 120 list of questions

Action: For adoption

3.3.7. - glycopyrronium bromide - EMEA/H/C/003883

treatment of sialorrhoea

Scope: Day 120 list of questions

Action: For adoption

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

3.4.1. - recombinant l-asparaginase - EMEA/H/C/002661

combination therapy for B/T cell lymphoblastic leukaemia (ALL) or B/T cell lymphoblastic lymphoma (LBL)

Scope: Letter from the applicant dated 5 June 2015 requesting an extension of clock stop to submit the responses to the D180 List of Outstanding Issues

Action: For adoption

List of Outstanding Issues adopted 21.05.2015. List of Questions adopted on 25.04.2014.

3.4.2. - susoctocog alfa – Orphan - EMEA/H/C/002792

Baxter AG; treatment of haemophilia A

Scope: Report from the BPWP

Action: For adoption

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

3.6. Initial applications in the decision-making phase

3.7. Withdrawals of initial marketing authorisation application

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. Norvir - ritonavir - EMEA/H/C/000127/X/0127

AbbVie Ltd.; the treatment of HIV-1, treatment of HIV-1 infection

Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Menno van der Elst

Scope: The MAH applies for a line extension of a new oral powder formulation of Norvir (ritonavir) as a replacement for the currently marketed Norvir oral solution for a more suitable ritonavir formulation for the paediatric population.

Action: For adoption

List of Outstanding Issues adopted on 26.03.2015. List of Questions adopted on 23.10.2014.

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

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. REVOLADE - eltrombopag / eltrombopag olamine - EMEA/H/C/001110/X/0022/G

Novartis Europharm Ltd

Rapporteur: Arantxa Sancho-Lopez, Co-Rapporteur: Greg Markey, PRAC Rapporteur: Dolores Montero Corominas

Scope: “Extension of indication for paediatric (age 1 year and above) chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins).

Grouping with the line extension for one new tablet strength (12.5mg) and a new Powder for Oral Suspension formulation (25mg).

The Type II variation and the Extension are grouped within this Application. This grouping is justified, as one of the variations in the group is an extension of the marketing authorisation (Annex III of Commission Regulation (EC) No 1234/2008 of November 2008). Agreed justification. 120 day TT follows Line extension."

Action: For adoption

Timetable:
Responses by: 18.10.2015
Restart: 19.10.2015
PRAC Rapporteur Assessment Report: 23.11.2015

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

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

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. Adcetris - brentuximab vedotin - Orphan - EMEA/H/C/002455/II/0025

Takeda Pharma A/S

Rapporteur: Pieter de Graeff, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Sabine Straus

Scope: "Extension of Indication to include new indication for Adcetris (ADCETRIS is indicated for the treatment of adult patients at increased risk of relapse or progression following ASCT"). 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."

Action: For adoption

5.1.2. Cervarix - human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - EMEA/H/C/000721/II/0067

GlaxoSmithKline Biologicals

Rapporteur: Daniel Brasseur, PRAC Rapporteur: Jean-Michel Dogné

Scope: “Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix.
As a consequence, sections 4.1, 4.8 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 update the RMP (v.11.0) including the new indication.”

Action: For adoption

5.1.3. Cosentyx - secukinumab - EMEA/H/C/003729/II/0001/G

Novartis Europharm Ltd

Rapporteur: Tuomo Lapveteläinen, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Dolores Montero Corominas

Scope: “Extension of Indication to include new indication for Cosentyx “treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate as monotherapy or in combination with methotrexate (MTX)”.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet is updated in accordance. Furthermore, minor editorial changes have been introduced throughout the PI and updated RMP has been also submitted.”

Action: For adoption

5.1.4. Cosentyx - secukinumab - EMEA/H/C/003729/II/0002

Novartis Europharm Ltd

Rapporteur: Tuomo Lapveteläinen, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Dolores Montero Corominas

Scope: “Extension of indication to add new indication for Cosentyx 'treatment of severe active ankylosing spondylitis in adults who have responded inadequately to conventional therapy'. Consequently SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 have been revised to include new efficacy and safety information. The Package Leaflet and RMP have been updated accordingly.” Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Action: For adoption

5.1.5. CYRAMZA - ramucirumab - Orphan - EMEA/H/C/002829/II/0004

Eli Lilly Nederland B.V.

Rapporteur: Pieter de Graeff, Co-Rapporteur: Kolbeinn Gudmundsson, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: “Extension of Indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes."

Action: For adoption

5.1.6. Edurant - rilpivirine - EMEA/H/C/002264/II/0017/G

Janssen-Cilag International N.V.

Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Sabine Straus

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

Action: For adoption

5.1.7. Eylea - aflibercept - EMEA/H/C/002392/II/0021

Bayer Pharma AG

Rapporteur: Pierre Demolis, Co-Rapporteur: Robert James Hemmings, PRAC Rapporteur: Arnaud Batz

Scope: "Extension of Indication to include a new indication for adult for the treatment of visual impairment due to myopic choroidal neovascularisation(myopic CNV).
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated. The Package Leaflet is updated in accordance.
In addition, some editorial changes are proposed in section 5.1 of the SmPC, in the Annex II and in the PL."

Action: For adoption

5.1.8. Humira - adalimumab - EMEA/H/C/000481/II/0137

AbbVie Ltd.

Rapporteur: Kristina Dunder, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Ulla Wändel Liminga

Scope: "This application seeks to add the following indication to section 4.1 of the SmPC for all presentations of Humira:
Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas. Consequential changes are proposed for

sections 4.2, 4.4, 4.8, 5.1 and 5.2. Changes reflecting the additions to the SmPC are proposed for sections 1 and 3 of the Package Leaflet."

Action: For adoption

Request for Supplementary Information adopted on 26.02.2015.

5.1.9. Kalydeco - ivacaftor - Orphan - EMEA/H/C/002494/II/0027

Vertex Pharmaceuticals (U.K.) Ltd.

Rapporteur: Concepcion Prieto Yerro, Co-Rapporteur: Melinda Sobor, PRAC Rapporteur: Miguel-Angel Macia

Scope: "Extension of indication for Kalydeco to include the treatment of cystic fibrosis in patients aged 18 years and older who have a R117H mutation in the CFTR gene. Consequently, changes are proposed to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and to the Package Leaflet."

Action: For adoption

Request for Supplementary Information adopted on 26.02.2015, 23.10.2014.

5.1.10. Levemir - insulin detemir - EMEA/H/C/000528/II/0070

Novo Nordisk A/S

Rapporteur: Jens Heisterberg

Scope: "Update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to extend the clinical use of Levemir in children from 2 years to 1 year of age.
The Package Leaflet is updated accordingly."

Action: For adoption

Request for Supplementary Information adopted on 26.03.2015.

5.1.11. Nplate - romiplostim - Orphan - EMEA/H/C/000942/II/0051

Amgen Europe B.V.

Rapporteur: Arantxa Sancho-Lopez, Co-Rapporteur: Pieter de Graeff, PRAC Rapporteur: Dolores Montero Corominas

Scope: "Extension of Indication to include second line treatment of all non-splenectomised patients (including those without a contraindication to surgery). As a consequence, section 4.1 of the SmPC has been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Croatia and Italy in the Package Leaflet."

Action: For adoption

5.1.12. Perjeta - pertuzumab - EMEA/H/C/002547/II/0010

Roche Registration Ltd;

Rapporteur: Christian Schneider, Co-rapporteur: Daniela Melchiorri, PRAC Rapporteur: Doris Stenver;

Scope: "The MAH is submitting a type II 90 day variation application to extend the use of Perjeta in combination with trastuzumab and docetaxel as part of a neoadjuvant treatment for patients with locally advanced, inflammatory or early stage HER2-positive breast cancer suitable for neoadjuvant therapy (tumours > 2 cm in diameter).

The submission is based primarily on the results of two randomized Phase II studies, NEOSPHERE (WO20697) and TRYPHAENA (BO22280).

The Perjeta annexes have been updated in the concerned sections as outlined below and in the SmPC track change version in Module 1.3.1.

The section 4.8 Undesirable effects of the SmPC (and the section 4 of the PIL accordingly) has been revised and includes now a pooled safety analysis across the studies CLEOPATRA, the pivotal study in metastatic breast cancer, and the two neoadjuvant studies NEOSPHERE and TRYPHAENA. A "Note to the Reviewer" providing further explanations on the pooled safety analysis is also included in the track change SmPC version in Module 1.3.1."

Action: For adoption

Request for Supplementary Information adopted on 21.05.2015, 18.12.2014.

5.1.13. Rebetol - ribavirin - EMEA/H/C/000246/II/0074

Merck Sharp & Dohme Limited

Rapporteur: Joseph Emmerich

Scope: "Change of the indication of Rebetol to reflect that ribavirine is indicated in the treatment of hepatitis C in combination with other medicinal products and remove reference to the peginterferon used (2a or 2b) in line with the PRAC recommendation in the PSUR assessment (EMEA/H/C/PSUSA/000100007/201307). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.7, 4.8, 4.9 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly."

Action: For adoption

Request for Supplementary Information adopted on 26.03.2015, 23.10.2014.

5.1.14. REVOLADE - eltrombopag / eltrombopag olamine - EMEA/H/C/001110/II/0020

Novartis Europharm Ltd

Rapporteur: Arantxa Sancho-Lopez, Co-Rapporteur: Greg Markey, PRAC Rapporteur: Dolores Montero Corominas

Scope: "Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to add a new indication on the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy. The package leaflet is updated accordingly. In addition, the MAH has corrected the acronym used for full blood counts (FBC) in the SmPC, Annex II and PL."

Action: For adoption

Request for Supplementary Information adopted on 26.02.2015.

5.1.15. REVOLADE - eltrombopag / eltrombopag olamine - EMEA/H/C/001110/II/0023

Novartis Europharm Ltd

Rapporteur: Arantxa Sancho-Lopez, Co-Rapporteur: Greg Markey, Scope: "Extension of Indication to extend the use of Revolade to non-splenectomized patients.
As a consequence, section 4.1 of the SmPC is updated. The Package Leaflet is updated in accordance."

Action: For adoption

5.1.16. Stayveer - bosentan - EMEA/H/C/002644/II/0011

Marklas Nederlands BV

Rapporteur: Pierre Demolis, PRAC Rapporteur: Arnaud Batz

Scope: "Update of SmPC sections 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 to reflect non-clinical and clinical data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04) in line with the recently approved application II-66 for Tracleer (bosentan). The Annex II and the Package Leaflet have been updated accordingly. Further, the MAH took the opportunity to make editorial changes in the SmPC and to update the contact details of the local representatives in the Package Leaflet. In addition, taking into account the new data in the paediatric population, an updated version of the RMP (version 7) aligned with RMP version 7 for Tracleer was provided."

Action: For adoption

5.1.17. Tysabri - natalizumab - EMEA/H/C/000603/II/0077

Biogen Idec Ltd

Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: "Extension of Indication to include new indication for Tysabri.
As a consequence, sections 4.1 and 4.4 of the SmPC are updated in order to provide physicians with more options for treating RRMS patients with high disease activity who fail an initial disease modifying therapy (DMT). Consequential changes to sections 4.2, 4.3, 5.1 and Package Leaflet in Sections 2 and 3 are also proposed."

Action: For adoption

5.1.18. Voncento - human coagulation factor viii / human von willebrand factor - EMEA/H/C/002493/II/0008/G

CSL Behring GmbH;

Rapporteur: Pieter de Graeff, Co-rapporteur: Greg Markey, PRAC Rapporteur: Sabine Straus;

Scope: "Extension of indication to include prophylactic treatment of patients with VWD. In addition the MAH is providing data to support treatment of paediatric patients with VWD."

Action: For adoption

Request for Supplementary Information adopted on 21.05.2015, 18.12.2014.

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

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

6.2. Update of Ancillary medicinal substances in medical devices

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)

7.1.1. Daclatasvir compassionate use - EMEA/H/K/0003867/OTH/0001

Daclatasvir for the use in combination with sofosbuvir +/- ribavirin, for genotype 1 adult patients at a high risk of decompensation or death within 12 months if untreated

Action: For adoption

Assessment Report

8. Pre-submission issues

8.1. Pre-submission issue

8.1.1. – Elotuzumab - Orphan - H0003967

Bristol-Myers Squibb Pharma EEIG, Treatment of multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received one or more prior therapies

Scope: Request for an accelerated review

Action: For adoption

Rapporteurs' accelerated assessment briefing note

Letter from the company dated 18 May requesting an accelerated review

8.1.2. Drisapersen Sodium - H0003846

Treatment of Duchenne Muscular Dystrophy (exon 51 mutation specific)

Scope: Request for an accelerated review

Action: For adoption

Rapporteurs' accelerated assessment briefing note

Letter from the company dated 18 May requesting an accelerated review

8.1.3. - Begelomab - Orphan - H0004144

ADIENNE S.r.l. S.U., indicated for the treatment of steroid resistant acute Graft-versus-Host Disease (GvHD) in adult patients who underwent allogeneic haematopoietic progenitor cell transplantation (HPCT) and received a standard immunosuppressive regimen

Scope: Request for an accelerated review

Action: For adoption

Letter from the company dated 4 May 2015 requesting an accelerated review

8.1.4. Grazoprevir/Elbasvir - Elbasvir\Grazoprevir - H0004126

Grazoprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, in combination with elbasvir, a HCV NS5A inhibitor, is indicated for the treatment of chronic hepatitis C (CHC) Genotypes 1, 4, and 6 infection

Scope: Request for an accelerated review

Action: For adoption

Letter from the company dated 5 June 2015 requesting an accelerated review

9. Post-authorisation issues

9.1. Post-authorisation issues

9.1.1. Pradaxa - dabigatran etexilate –EMEA/H/C/000829/ LEG 043 and LEG2 043.1; Xarelto – Rivaroxaban – EMEA/H/C/000944/LEG; Eliquis – Apixaban – EMEA/H/C/002148/LEG; Lixiana – Edoxaban – EMEA/H/C/002629/LEG

Boehringer Ingelheim International GmbH (Pradaxa), Bayer Pharma AG (Xarelto), Bristol-Myers Squibb / Pfizer (Eliquis), Daiichi Sankyo Europe GmbH (Lixiana)

Lead Rapporteur: Jens Heisterberg,
Rapporteurs: Joseph Emmerich, Rafe Suvarna, Kristina Dunder, Martina Weise, Pieter de Graeff, Concepcion Prieto Yerro, EPL: Catherine Drai, Anna Baczynska

Scope: New oral anticoagulants - LEGs

Action: For discussion

9.1.2. Kolbam - Cholic Acid - Orphan - EMEA/H/C/002081

ASK Pharmaceuticals GmbH, treatment of inborn errors of primary bile acid synthesis

Rapporteur: Robert James Hemmings, Co-Rapporteur: Patrick Salmon,

Scope: Update on licensing status

Action: For discussion

New active substance (Article 8(3) of Directive No 2001/83/EC)

9.1.3. Mysimba - Naltrexone/Bupropion – EMEA/H/C/003687/ANX 001

Orexigen Therapeutics Ireland Limited, indicated for the management of obesity

Rapporteur: Jens Heisterberg, Co-Rapporteur: Robert James Hemmings, PRAC Rapporteur: Martin Huber,

Scope: PASS protocol review, Request for Supplementary Information, PRAC advice

PRAC consultation on a PASS protocol for a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects

Action: For adoption

9.1.4. CellCept - Mycophenolate Mofetil,Mycophenolate Mofetil Hydrochloride - EMEA/H/C/000082

Roche Registration Ltd, prophylaxis of acute transplant rejection

Rapporteur: Rafe Suvarna, Co-Rapporteur: Patrick Salmon,

Action: For discussion

9.1.5. TECFIDERA - Dimethyl Fumarate - EMEA/H/C/002601/WS0689/G; NAPs included in WS: Fumaderm, Fumaderm Intial

MAH: Biogen Idec Ltd, treatment of multiple sclerosis

Rapporteur: Martina Weise, Co-Rapporteur: Robert James Hemmings,

Report from SAG Neurology held on 11 June 2015.

Action: For discussion

9.1.6. Rotarix - human rotavirus, live attenuated - EMEA/H/C/000639/II/0062

GlaxoSmithKline Biologicals S.A.,

Rapporteur: Daniel Brasseur, PRAC Rapporteur: Jean-Michel Dogné,

Scope: Opinion, VWP Report
"To submit the final report of genetic stability study EPI-ROTA-014 VS BE – 112560 that addresses the Post-Approval Measure ME2 005.2 in which the MAH commits to monitor for the potential occurrence of genetic drifts and shifts in the vaccine strain in post-marketing settings." Request for Supplementary Information adopted on 24.07.2014, 20.03.2014.

Action: For discussion

9.1.7. Picato - ingenol mebutate - EMEA/H/C/002275/II/0012

Leo Pharma A/S

Rapporteur: Robert James Hemmings,

Scope: Opinion, RSI
"Update sections 4.2, 4.8 and 5.1 to provide new efficacy and safety data supporting a labelling update that introduces repeat treatment of Picato gel (150 mcg/g and 500 meg/g), based on Trial LP0041-22. The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor linguistic amendments."

Request for Supplementary Information adopted on 23.04.2015.

Action: For adoption

10. Referral procedures

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

10.1.1. Canagliflozin – INVOKANA- EMEA/H/C/002649; canagliflozin, metformin – VOKANAMET - EMEA/H/C/002656; dapagliflozin – FORXIGA - EMEA/H/C/002322; dapagliflozin, metformin – XIGDUO - EMEA/H/C/002672; empagliflozin - JARDIANCE - EMEA/H/C/002677; empagliflozin, metformin – SYNJARDY EMEA/H/C/003770

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

Rapporteurs: Martina Weise, Kristina Dunder, Filip Josephson, Agnes Gyurasics, Pieter de Graeff, Bart Van der Schueren, Daniela Melchiorri

Scope: Signal of diabetic ketoacidosis - start of Article 20 referral at PRAC

Action: For information

10.1.2. Medicinal products under development for the treatment of Ebola (EMEA/H/A-5(3)/1410)

Scope: Assessment timetable

Action: Adopted by written procedure

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

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

10.3.1. IOGOL and associated names soft capsules, 25 / 50 mg - diclofenac epolamine - EMEA/H/A-29/1414)

Regiomedica GmbH

Rapporteur: Martina Weise, Co-Rapporteur: Concepcion Prieto Yerro,

Scope: List of Outstanding Issues

Disagreements regarding the demonstration of bioequivalence with the reference product

Action: For adoption

RMS: DE, CMS: AT, BE, CZ, EL, ES, HU, IT, PL, SK, UK, Decentralised procedure number:

DE/H/3633/002-003/DC

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

10.4.1. Amoxil - amoxicillin - EMEA/H/A-30/1372

GlaxoSmithKline

Rapporteur: Robert James Hemmings, Co-Rapporteur: Concepcion Prieto Yerro,

Scope: Opinion or List of Outstanding Issues

Harmonisation exercise for Amoxil and associated names. The review was triggered by the European Commission, due to the need of harmonisation of the Summary of Product Characteristics across Member State

Action: For adoption

List of Questions adopted on 25.07.2013. List of Outstanding Issues adopted 25.04.2014, 23.10.2014, 26.02.2015.

10.4.2. Clenil and associated names - Beclometasone dipropionate - EMEA/H/A-30/xx

Chiesi group of companies and associated companiesScope: Appointment of Rapporteurs. Adoption of List of Questions and timetable.

Harmonisation exercise for Clenil and associated names (beclometasone dipropionate). The review was triggered by Italy due to the need to harmonise the product information across all Member States, including the therapeutic indication, the target populations and the posology recommendations.

Action: For adoption

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

10.5.1. Adrenaline auto injectors (EMEA/H/A-31/1398)

Rapporteur: Alar Irs, Co-Rapporteur: Robert James Hemmings,

Scope: Opinion or possible oral explanation

Article 31 triggered by the MHRA due to the lack of robust evidence that the devices deliver the adrenaline intramuscularly in all patients.

Action: For adoption

List of Outstanding Issues adopted on 26.02.2015 and 25.09.2014. Ad-hoc expert group meeting held on 23 January 2015.

See 2.4.1

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

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

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

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

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

11. Pharmacovigilance issue

11.1. Early Notification System

June 2015 Early Notification System on Envisaged CHMP Recommendations for Regulatory Action (based on Identified Safety Concerns) Accompanied by Communication to the General Summary of recommendations and advice of PRAC meeting held on 08-11 June 2015.

Action: For information

11.1.1. Gilenya - Fingolimod Hydrochloride - EMEA/H/C/002202

Novartis Europharm Ltd, treatment of multiple sclerosis

Rapporteur: Pierre Demolis, Co-Rapporteur: Filip Josephson,

Scope: Report SAG/ad hoc expert advisory group for fingolimod held 11 June 2015

Action: For discussion

12. Inspections

12.1. GMP inspections

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

12.2. GCP inspections

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

12.3. Pharmacovigilance inspections

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

12.4. GLP inspections

Disclosure of 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

Disclosure of information related to briefing meetings taking place with applicants cannot be released at present time as deemed to contain commercially confidential information

13.2.1 ITF Briefing Meeting

Action: For adoption

13.2.2 ITF Briefing Meeting

Action: For adoption

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

13.4. Nanomedicines activities

14. Organisational, regulatory and methodological matters

14.1. Mandate and organisation of the CHMP

14.1.1. Strategic Review & Learning Meetings

Outcome and follow-up items from the Strategic review and learning Joint CHMP and CAT Meeting under Latvian Presidency, Ljubljana, Slovenia held on 26-28 May 2015

Action: For information

Presentations from the meeting

14.1.2. CHMP plenary 17-20 August 2015 to be replaced by CHMP written procedure

Action: For adoption

Timetable for August 2015 written procedure

14.2. Coordination with EMA Scientific Committees

14.2.1. Pharmacovigilance Risk Assessment Committee (PRAC)

Summary of recommendations and advice of PRAC meeting held on 08-11 June 2015

Action: For information

List of Union Reference Dates and frequency of submission of Periodic Safety Update Reports (EURD list) for June 2015

Action: For adoption

14.2.2. Committee for Advanced Therapies (CAT)

CAT draft minutes of meeting held on 18-19 June 2015
Action: For information

14.2.3. Committee for Herbal Medicinal Products (HMPC)

Report from the HMPC meeting held on 4-7 May 2015

Action: For information

Letter from HMPC concerning the toxicological assessment of pulegone / menthofuran and consequences for medicinal products containing menthae piperitae aetheroleum

Action: For Discussion

14.2.4. Paediatric Committee (PDCO)

PIPs reaching D30 at June 2015 PDCO

Action: For information

Report from the PDCO meeting held on 17-19 June 2015

Action: For information

PIP: Expected key elements and requirements for a new DTaP-containing combination vaccine

Answers to public comments and final document

Action: For adoption

14.2.5. Committee for Orphan Medicinal Products (COMP)

Report from the COMP meeting held on 16-17 June 2015
Action: For information

14.2.6. CMDh

Report from the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on the meeting held on 22-24 June 2015

Action: For information

Letter from CMD(h) dated 29 May 2015 to CHMP (PKWP / MSWG) on biowaiver justification – Rosuvastatin 1ApHarma

Action: For discussion

Question to CHMP (PKWP / MSWG) on biowaiver justification – Rosuvastatin 1ApHarma

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

14.3.1. Scientific Advice Working Party (SAWP)

Report from the SAWP meeting held on 1-3 June 2015. 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.

14.3.2. Invented name issues

Table of Decisions of the NRG meeting held on 20 May 2015.

Action: For adoption

14.3.3. Quality Working Party (QWP)

Q&A on complex manufacturing processes (EMA/CHMP/CVMP/QWP/390257/2015)

Action: For adoption

14.3.4. Gastroenterology Drafting Group

Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing

Action: For adoption

Guideline coming into effect on 1 January 2016.

14.3.5. Biostatistics Working Party (BSWP)

Nomination of Mr Jiri Haman (CZ) as observer to Biostatistics Working Party

Action: For adoption

14.4. Cooperation within the EU regulatory network

14.5. Cooperation with International Regulators

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

14.7. CHMP work plan

14.7.1. CHMP Work Plan 2015 - update on activities

Action: **For information**

14.7.2. Planning and reporting

2015 initial MAA submissions with appointed Rapporteur

Q2-15 planning update

Action: For information

14.8. Others

15. Any other business

15.1. Revision of the Accelerated Assessment guideline

Action: For discussion

15.2. Enhanced early dialogue to foster development and facilitate accelerated assessment

Action: For discussion

15.3. Patient involvement in benefit and risk assessment of medicinal products

Action: For discussion

15.4. Committee update on CHMP/PRAC Liaison person for the PRAC-led variations

Action: For discussion

15.5. Update of CHMP D210 AR template for initial marketing authorisation applications

Action: For adoption

15.6. First draft of Scientific Guidance on Post-authorisation Efficacy Studies (PAES)

Action: For information

15.7. Feedback on Early Background Summaries

Action: For discussion

15.8. Expertise of CHMP members and alternates

Action: For agreement

16. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

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)*

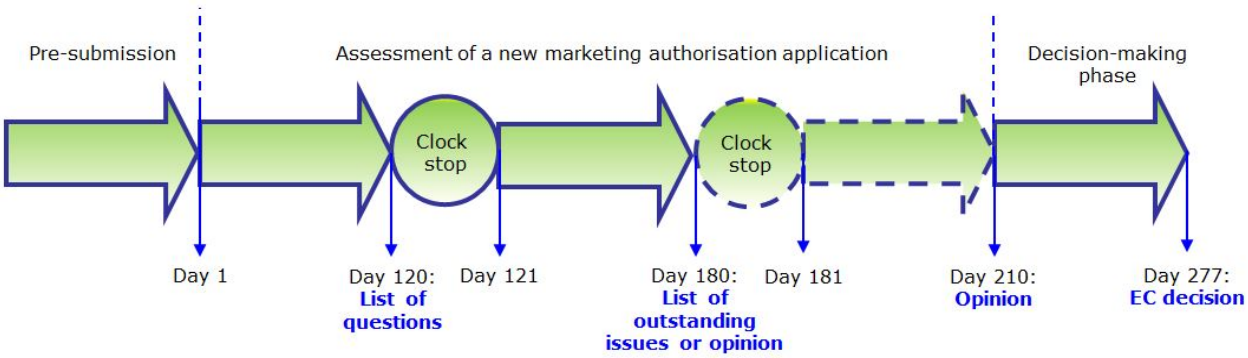
The items listed in this section are those for which marketing authorisation holders (MAHs) or applicants have been invited to the CHMP plenary meeting to address questions raised by the Committee. Oral explanations normally relate to on-going applications (section 3, 4 and 5) or referral procedures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