20 April 2015
EMA/CHMP/206325/2015
Procedure Management and Business Support Division

Committee for medicinal products for human use (CHMP)

Agenda of meeting to be held on 20-23 April 2015

Chair: Tomas Salmonson – Vice-chair: Pierre Demolis

20 April 2015, 13:00 – 19:30, room 2A

21 April 2015, 08:30 – 19:30, room 2A

22 April 2015, 08:30 – 19:30, room 2A

23 April 2015, 08:30 – 16:00, room 2A

Note on access to documents

Some documents mentioned in the agenda/minutes cannot be released at present following a request for access to documents under 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).

Health & 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 and therefore not disclosed. With regards to therapeutic indications 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. The procedures discussed by the CHMP are on-going and therefore are considered confidential. 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. For orphan medicinal products the applicant details are published as this information is already publicly available.

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

Further information with relevant explanatory notes can be found at the end of this document.

For adoption

Agenda (EMA/CHMP/206325/2015 rev.4) and Annex to CHMP agenda of the CHMP plenary session to be held 20-23 April 2015.	
Timeschedule (EMA/CHMP/223425/2015 rev.3) of the CHMP plenary session to be held 20-23 April 2015.	
Minutes ((EMA/CHMP/223528/2015 rev. 0) of the CHMP plenary session held 23-26 March 2015.	

For information

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 20-23 April 2015	*See April 2015 Minutes (to be published post May 2015 CHMP meeting)*
Draft Agenda of CHMP meeting to be held on 18-21 May 2014.	

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1. Oral explanations

1.1. Pre-authorisation procedure oral explanations

(EMEA/H/C/003766), (evolocumab), (Hypercholesterolaemia and mixed dyslipidaemia and Homozygous familial hypercholesterolaemia) List of Questions adopted on 22.01.2015. • BWP Report: **For adoption**	Possible oral explanation on Tuesday 21 April 2015 at 11.00.
(EMEA/H/C/003702), (phenylephrine hydrochloride / ketorolac trometamol), (maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement (ILR) in adults) List of Outstanding Issues adopted on 22.05.2014. List of Questions adopted on 23.01.2014.	Possible oral explanation on Wednesday 22 April 2015 at 11.00.

1.2. Re-examination procedure oral explanation

1.3. Post-authorisation procedure oral explanation

Somavert (EMEA/H/C/000409/X/0072), (pegvisomant), MAH: Pfizer Limited, Rapporteur: Pierre Demolis, PRAC Rapporteur: Arnaud Batz, "Addition of 25 mg and 30 mg powder and solvent for solution for injection." List of Outstanding Issues adopted on 26.02.2015. List of Questions adopted on 25.09.2014. • Similarity Assessment Report: **For adoption** • BWP Report: **For adoption**	Possible Oral Explanation on Tuesday 21 April 2015 at 14.00.

1.4. Referral procedure oral explanation

2. Initial applications

2.1. Initial applications; Opinions

(EMEA/H/C/003803), (aripiprazole), (treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder)

List of Outstanding Issues adopted on 26.02.2015.
List of Questions adopted on 20.11.2014.

(EMEA/H/C/003899), (aripiprazole), (treatment of schizophrenia and prevention of manic episodes in bipolar I disorder)

List of Outstanding Issues adopted on 26.02.2015.
List of Questions adopted on 20.11.2014.

(EMEA/H/C/002772), Orphan, (dasiprotimut-t), Applicant: Biovest Europe Ltd, (treatment of non-Hodgkin's lymphoma (FL))

Oral explanation was held on 24 March 2015. List of Outstanding Issues adopted on 18.12.2014.
List of Questions adopted on 25.04.2014.

- BWP Report: **For adoption**

(EMEA/H/C/003981), (duloxetine), (treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder, treatment of major depressive episodes, diabetic peripheral neuropathic pain and generalised anxiety disorder)

List of Outstanding Issues adopted on 26.03.2015. List of Questions adopted on 22.01.2015.

(EMEA/H/C/003870), Orphan, (tasimelteon), Applicant: Vanda Pharmaceuticals Ltd., (treatment of Non-24-Hour Sleep-Wake Disorder (Non-24))

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

(EMEA/H/C/002629), (edoxaban), (prevention of stroke; embolism and treatment of venous thromboembolism)

Oral explanation was held on 24 February 2015.
List of Outstanding Issues adopted on 26.02.2015, 22.01.2015, 20.11.2014.
List of Questions adopted on 26.06.2014.

(EMEA/H/C/002749), (lutetium, isotope of mass 177), (used only for the radiolabelling of carrier molecules)

List of Outstanding Issues adopted on 26.02.2015.
List of Questions adopted on 26.06.2014.

(EMEA/H/C/003985), (nivolumab), (treatment of advanced (unresectable or metastatic) melanoma in adults.)

List of Questions adopted on 22.01.2015.

- BWP Report: **For adoption**

(EMEA/H/C/003962), (pregabalin), (treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD))

List of Outstanding Issues adopted on 26.02.2015.
List of Questions adopted on 18.12.2014.

(EMEA/H/C/004078), (pregabalin), (treatment of epilepsy and generalised anxiety disorder (GAD))

List of Outstanding Issues adopted on 26.02.2015.
List of Questions adopted on 18.12.2014.

(EMEA/H/C/004010), (pregabalin), (treatment of neuropathic pain, epilepsy and generalised anxiety disorder)

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

(EMEA/H/C/004070), (pregabalin), (treatment of epilepsy and generalised anxiety disorder (GAD))

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

2.2. Initial applications; Day 180 List of outstanding issues

(EMEA/H/C/003935), (duloxetine), (Treatment depressive disorder, diabetic neuropathic pain, anxiety disorder, treatment depressive disorder, diabetic neuropathic pain, anxiety disorder)

List of Questions adopted on 22.01.2015.

(EMEA/H/C/003820), (pembrolizumab), (treatment of melanoma)

List of Questions adopted on 23.10.2014.

- BWP Report: **For adoption**

(EMEA/H/C/002792), Orphan, (susoctocog alfa), Applicant: Baxter AG, (treatement of haemophilia A)

List of Questions adopted on 20.11.2014.

BWP Report: **For adoption**

(EMEA/H/C/002839), (sonidegib), (treatment of basal cell carcinoma (BCC))

List of Questions adopted on 25.09.2014.

(EMEA/H/C/002739), (human alpha1-proteinase inhibitor), (treatment of lung disease)

The ad-hoc expert group meeting held on. List of Outstanding Issues adopted on26.03.2015 and 20.11.2014.
List of Questions adopted on 25.04.2014.

BWP Report: **For adoption**

2.3. Initial applications; Day 120 List of Questions

(EMEA/H/C/003898), (brivaracetam), (treatment of partial-onset seizures)

(EMEA/H/C/004042), (elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide), (treatment of HIV-1)

(EMEA/H/C/004104), (eptifibatide), (prevention of early myocardial infarction)

(EMEA/H/C/002733), (ferric maltol), (treatment of iron deficiency anaemia)

(EMEA/H/C/004147), (octocog alfa), (treatment and prophylaxis of haemophilia A, treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency))

- BWP Report: **For adoption**

(EMEA/H/C/003825), (octocog alfa), (treatment and prophylaxis of haemophilia A, treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency))

- BWP Report: **For adoption**

(EMEA/H/C/002790), (opicapone), (Parkinson's disease and motor fluctuations)

(EMEA/H/C/004114), (pemetrexed), (treatment of malignant pleural mesothelioma and non-small cell lung cancer)

(EMEA/H/C/003886), (necitumumab), (treatment of squamous non-small cell lung cancer)

- BWP Report: **For adoption**

(EMEA/H/C/003882), (alirocumab), (reduction of low-density lipoprotein cholesterol (LDL-C) and increase high-density lipoprotein cholesterol (HDL-C).)

- BWP Report: **For adoption**

(EMEA/H/C/004004), Orphan, (sebelipase alfa), Applicant: Synageva BioPharma Ltd, (treatment of enzyme replacement therapy (ERT))

- BWP Report: **For adoption**

(EMEA/H/C/004007), (etanercept), (treatment of arthritis)

- BWP Report: **For adoption**

(EMEA/H/C/003774), Orphan, (selexipag), Applicant: Actelion Registration Ltd., (treatment of pulmonary arterial hypertension (PAH; WHO Group I))

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

(EMEA/H/C/003938), (betulae cortex dry extract (5-10 : 1); extraction solvent: n-heptane 95% (w/w)), (treatment of partial thickness wounds)

- Similarity Assessment Report: **For adoption**
- Letter from the applicant dated 9 April 2015 requesting an extension of clock stop to submit the responses to the D120 List of Questions : **For adoption**

(EMEA/H/C/003790), Orphan (Carfilzomib), Applicant: Amgen Europe B.V., (treatment of multiple myeloma),

- Similarity Assessment Report**: For adoption**

(EMEA/H/C/003750), Orphan, ATMP, (allogenic human heterologous liver cells), Applicant: Cytonet GmbH&Co KG, (treatment of urea cycle disorders (UCD)), List of Outstanding Issues adopted on 18.12.2014. List of Questions adopted on 25.04.2014.

- Update on procedure following oral explanation / discussion at CAT

(EMEA/H/C/003776), (ferric citrate coordination complex), (treatment of hyperphosphataemia)
List of Questions adopted on 24.07.2014. List of Outstanding Issues adopted on 26.03.2015

- Letter from the Applicant received 1 April 2015 requesting extension of the clock-stop for submission of responses to Day 180 List of Outstanding Issues: **For adoption**

(EMEA/H/C/003759), (guanfacine), (treatment of ADHD)
List of Questions adopted on 24.07.2014.

- List of Questions to SAG Psychiatry : **For adoption**

(EMEA/H/C/003725), Orphan, (panobinostat), Applicant: Novartis Pharmaceuticals UK Limited, (treatment of multiple myeloma)
List of Questions adopted on 25.09.2014.

- List of experts to SAG Oncology meeting: **For adoption**

(EMEA/H/C/003926), (aripiprazole), (treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder)

2.5. Products in the Decision Making Phase

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

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

Orfadin (EMEA/H/C/000555/X/0041), Orphan, (nitisinone), MAH: Swedish Orphan Biovitrum International AB, Rapporteur: Luca Pani, PRAC Rapporteur: Carmela Macchiarulo, "To add an oral suspension 4 mg/ml as additional pharmaceutical form"
List of Outstanding Issues adopted on 23.10.2014.
List of Questions adopted on 19.12.2013.

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

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

Emend (EMEA/H/C/000527/X/0049/G), (aprepitant), MAH: Merck Sharp & Dohme Limited, Rapporteur: Filip Josephson, Co-Rapporteur: Pieter de Graeff, PRAC Rapporteur: Ulla Wändel Liminga, "The MAH has submitted a type II variation classified as C.I.6 to extend the indication for chemotherapy-induced nausea and vomiting (CINV) in adults to paediatric patients (12 to 17years) for the 80mg and 125mg hard capsules. SmPC section 4.2 and 5.3 of the 165mg hard capsule label, which is consequential to the outcome of this grouped procedure, will be updated under the scope of type II variation classified as C.I.6.

In addition to this, an application for an addition of a new pharmaceutical form (powder for oral suspension) has been submitted for 125mg stength as part of this grouping.

The MAH has also submitted a type II variation classified as C.I.4 to reflect the paediatric results for prevention of post-operative nausea and vomiting (PONV) in the clinical sections of 40mg hard capsules label, thus updating sections 5.1 and 5.2 of the SmPC.

The Package Leaflet has been proposed to be updated accordingly."

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

4. Type II variations - Extension of indication procedures according to Annex I of Commission Regulation (EC) No 1234/2008

4.1. Type II variation; Extension of indication- Opinions or Requests for supplementary information

Esmya (EMEA/H/C/002041/II/0028), (ulipristal), MAH: Gedeon Richter Plc., Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, "Update of section 4.1 of the SmPC with subsequent updates to sections 4.2, 4.4, 4.8 and 5.1 in order to extend the current indication to long term (repeated intermittent) treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The Package Leaflet is updated accordingly." Request for Supplementary Information adopted on 26.02.2015, 20.11.2014.	
Invega (EMEA/H/C/000746/II/0043), (paliperidone), MAH: Janssen-Cilag International N.V., Rapporteur: Filip Josephson, PRAC Rapporteur: Qun-Ying Yue, "Update of sections 4.1 of the SmPC in order to extend the Invega indication to include depressive symptom domain of schizoaffective disorder. Additionally section 5.1 has been updated to reflect the data from the study SCA-3004 on paliperidone palmitate effects in the maintenance of symptom control. Minor editorial changes have been introduced throughout the PI. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet." Request for Supplementary Information adopted on 20.11.2014.	

Kuvan (EMEA/H/C/000943/II/0033), Orphan, (sapropterin), MAH: Merck Serono Europe Limited, Rapporteur: Patrick Salmon, Co-Rapporteur: Daniel Brasseur, “Extension of indication for the 'treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of 4 years of age and over with phenylketonuria (PKU) who have shown to be responsive to such treatment' to include the paediatric population under 4 years old. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated accordingly.”
Levemir (EMEA/H/C/000528/II/0071), (insulin detemir), MAH: Novo Nordisk A/S, Rapporteur: Jens Heisterberg, Co-Rapporteur: Pieter de Graeff, “Extension of Indication to include new indication for Levemir. As a consequence, sections 4.2, 4.5 and 5.1 of the SmPC are updated in order to update the safety information. The Package Leaflet is updated in accordance.”

Pyramax (EMEA/H/W/002319/II/0002), (pyronaridine / pyronaridine phosphate / artesunate), MAH: Shin Poong Pharmaceutical Co., Ltd., Rapporteur: Joseph Emmerich, Co-Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Arnaud Batz, "x To amend SmPC section 4.1 (Therapeutic Indications) to remove restrictions on repeated course of treatment in any individual and use only in areas of low transmission with evidence of artesmisinin resistance, based on further clinical experience. Consequent changes in SmPC sections 4.2 (Posology), 4.4 (Special warnings and precautions), 4.8 (Undesirable effects) and the PL are also included.
A recommended change is made to SmPC Section 4.2 (Posology) in relation to dosing in mild to moderate renal impairment.
A minor editorial adjustment is proposed to SmPC section 5.1 (Pharmacodynamic properties)."
Request for Supplementary Information adopted on 18.12.2014, 26.06.2014.

- Report from SAG anti-infectives meeting held on 30 March 2015: **For discussion**

Relistor (EMEA/H/C/000870/II/0030), (methylnaltrexone bromide), MAH: TMC Pharma Services Ltd, Rapporteur: Harald Enzmann, Co-Rapporteur: Greg Markey, PRAC Rapporteur: Valerie Strassmann, "The MAH applied for an extension of the indication for the treatment of opioid induced constipation in adult non cancer pain patients. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance."
Request for Supplementary Information adopted on 20.11.2014, 26.06.2014.
Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Resolor (EMEA/H/C/001012/II/0034), (prucalopride), MAH: Shire Pharmaceuticals Ireland Ltd., Rapporteur: Greg Markey, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Rafe Suvarna, "This type II variation (category

C.I.6) is provided on the basis of the completion of the clinical study SPD555-302. Following a meeting with the Resolor Rapporteur on 11 March 2014 it was agreed that the results of SPD555-302 would be provided to the EMA for assessment no later than 30 September 2014. The conduct and conclusion of study SPD555-302 was completed as a Post Approval Commitment (FUM 004 (MEA 004.2)) - To perform an efficacy study in males.
Based on the results from study SPD555-302, the MAH has submitted this type II variation to extend the indication for Resolor into the male population. The results of study SPD555-302 will be reflected in the Annex (a clean and track change version of the Resolor SmPC and PIL are provided for review). Throughout section 5.1 (Pharmacodynamic properties) of the SmPC the MAH has replaced the name of
the active “prucalopride” with “Resolor” for consistency and accuracy in this section.
In support of the proposed update to the Resolor SmPC a Phase 1 Study (SPD555-104) to Investigate the Absorption, Metabolism, and Excretion of [14C] Prucalopride Succinate Following a Single Oral Dose in Healthy Male Subjects has also been provided with this variation.
In support of the proposed amendment to section 4.1 (Therapeutic indications) of the SmPC the MAH also intends to apply for extended data/market exclusivity Under Article 14 (11) of Regulation (EC) No 726/2004 or Article 10 (1) fourth subparagraph of Directive 2001/83/EC. The Marketing Authorisation Holder (MAH) hereby applies for an additional 1 year of marketing protection and supporting documentation is thus provided in module 1.5.3.
An updated Risk Management Plan (RMP) (version 12) is also provided with this submission. The updated RMP is provided following the finalisation of study SPD555-302 for the male population and also following a request from the Rapporteur during the assessment of the PSUR 007 (EMEA/H/C/1012/ PSU
021) to include the important potential risk “Increase in prolactin levels”.
Separate to the update of the Resolor Annex

with an update to the therapeutic indication, the MAH also proposes changes to section 6 of the Patient Information Leaflet with the revision of the contact details (address and/or telephone numbers for the local representatives in Belgium and Italy." Request for Supplementary Information adopted on 18.12.2014. Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)	
Tygacil (EMEA/H/C/000644/II/0092), (tigecycline), MAH: Pfizer Limited, Rapporteur: Arantxa Sancho-Lopez, PRAC Rapporteur: Miguel-Angel Macia, "Addition of a new restricted indication in children eight year-old and older. The sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated accordingly. The Package Leaflet is also updated. In addition, an updated RMP is proposed." Request for Supplementary Information adopted on 23.03.2015.	
Vidaza (EMEA/H/C/000978/II/0030), Orphan, (azacitidine), MAH: Celgene Europe Limited, Rapporteur: Pieter de Graeff, Co-Rapporteur: Arantxa Sancho-Lopez, PRAC Rapporteur: Sabine Straus, "Extension of Indication to add treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification, based on the pivotal phase III study AZA- AML-001. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 10.0 was provided as part of the application. The application includes a request for an additional year of market protection for a new indication in accordance with Article 10(1) of Directive 2001/83/EC." Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)	

4.2. Update on on-going type II variation; extension of indications

Qutenza (EMEA/H/C/000909/II/0039), (capsaicin), MAH: Astellas Pharma Europe B.V., Rapporteur: Bruno Sepodes, Co-Rapporteur: Melinda Sobor, PRAC Rapporteur: Magda Pedro, , "Extension of indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE). As a consequence sections 4.1, 4.4 and 4.8 of the SmPC have been updated, and Annex II (additional risk minimisation measures) and the Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and Package Leaflet. An updated RMP (version 18) was provided as part of the application. The provision of studies STEP and PACE addresses MEA 001.4."

- Letter from the applicant dated 31 March 2015 requesting extension of clock stop to submit the responses to the Request for Supplementary Information adopted on 23.03.2015 : **For information**

5. Ancillary medicinal substances in medical devices

5.1. Ancillary medicinal substances in medical devices - Opinions/ List of outstanding issues / List of Questions

(EMEA/H/D/003740), (human serum albumin), (the storage, manipulation, in-vitro culture and transfer of human gametes)
List of Outstanding Issues adopted on 26.02.2015, 18.12.2014, 25.09.2014.
List of Questions adopted on 23.01.2014.

- Opinion: **For adoption**
- BWP Report: **For adoption**

6. Re-examination procedure (new applications) under Article 9(2) of Regulation no 726/2004

7. Re-examination procedure (Type II variations) under Article 16 of Commission Regulation (EC) No 1234/2008 and 9(2) of Regulation (EC) No 726/2004

8. Withdrawal of full initial application

(EMEA/H/C/004009), (duloxetine), (treatment in adults of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder.)

List of Questions adopted in January 2015.

- Letter from the applicant dated 08.04.2015 informing of the withdrawal of the marketing authorisation application: **For information**

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

10. Pre-submission issues

Some items in this section are considered commercially confidential or sensitive and therefore not disclosed.

(H0003854)
(Autologous CD34+ Cells Transduced with Retroviral Vector Containing the Adenosine Deaminase Gen), (Severe combined immunodeficiency due to adenosine deaminase deficiency), **ATMP**

- CAT recommendation on request for accelerated review: **For discussion**

11. Post-authorisation issues

Some items in this section are considered commercially confidential or sensitive and therefore not disclosed.

WS0689/G
TECFIDERA-
EMEA/H/C/002601/WS0689/0011/G
NAPs included in WS: Fumaderm, Fumaderm Intial (fumarate containing products), MAH: Biogen Idec Ltd, Rapporteur: Martina Weise, PRAC Rapporteur: Martin Huber, "Update of sections 4.4 of the SmPC in order to add a recommendation to consider interruption of treatment in patients with low lymphocyte counts (<0.5 x 109/L) persisting for more than six months and to monitor lymphocyte counts until recovery. Update of section 4.8 of the SmPC with information on observed low lymphocyte counts in clinical studies with tecfidera and PML (Progressive multifocal leukoencephalopathy) occurrence in the setting of severe and prolonged lymphopenia. Furthermore, the due dates of two commitments as part of the RMP have been revised." Request for Supplementary information adopted on 26.02.2015.

- Request for Supplementary information / Opinion : **For adoption**

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Infanrix hexa (EMEA/H/C/000296)
(Diphtheria Toxoid Adsorbed,Filamentous Haemagglutinin,Pertussis Toxoid Adsorbed,Poliovirus Type 1 (Inactivated),Poliovirus Type 2 (Inactivated),Poliovirus Type 3 (Inactivated),Pertactin,Tetanus Toxoid Adsorbed,Haemophilus Influenzae Type B Polysaccharide, Adsorbed,Hepatitis B, Recombinant Surface Antigen, Adsorbed), MAH: GlaxoSmithKline Biologicals, Rapporteur: Daniel Brasseur, Co-Rapporteur: Jan Mueller-Berghaus,

- Letter to GSK Biologicals concerning the batch release testing and the application of 3Rs methods: **For adoption**

Hexacima (EMEA/H/C/002702)
(Diphtheria Toxoid,Filamentous Haemagglutinin,Hepatitis B Surface Antigen,Pertussis Toxoid,Tetanus Toxoid,Haemophilus Influenzae Type B Polysaccharide,Polyribosylribitol Phosphate Conjugated To Tetanus Protein,Type 1 (Mahoney),Type 2 (Mef-1),Type 3 (Saukett)), MAH: Sanofi Pasteur, Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Daniel Brasseur,

- Letter to Sanofi Pasteur concerning the batch release testing and the application of 3Rs methods: **For adoption**

Bronchitol (EMEA/H/C/001252/II/0016/G), Orphan, (mannitol), MAH: Pharmaxis Pharmaceuticals Limited, Rapporteur: Robert James Hemmings, "Update of the condition reported in annex II D of the product information in order to update the protocol condition on patients recruitment and consequentially to postpone the final study report due date.

- Request for Supplementary information / Opinion : **For adoption**

Glybera (EMEA/H/C/002145/II/0038), Orphan, (alipogene tiparvovec), MAH: uniQure biopharma B.V., Rapporteur: Elaine French, CHMP Co-ordinator: Greg Markey, "Update of section 5.1 of the SmPC based on the final CSR for Study CT-AMT-011-05, a retrospective clinical records review study undertaken to generate further long-term follow-up data on the incidence and severity of acute pancreatitis episodes in LPLD subjects who previously participated in clinical studies with alipogene tiparvovec or AMT-10."Request for Supplementary Information adopted on 20.11.2014.

- Request for Supplementary information / Opinion : **For adoption**

Daklinza (EMEA/H/C/003768)
(Daclatasvir Dihydrochloride), MAH: Bristol-Myers Squibb Pharma EEIG, Rapporteur: Filip Josephson, Co-Rapporteur: Robert James Hemmings, (treatment of chronic hepatitis C virus
treatment of chronic hepatitis C virus (HCV)), New active substance (Article 8(3) of Directive No 2001/83/EC)

Signal of arrhythmia

12. Referral procedures

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

12.2. Requests for CHMP Opinion under Article 5(3) and 57 (1)p of Regulation (EC) No 726/2004

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

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

MERISONE 50 mg and 150 mg film coated tablets and MYOSON 50 mg and 150 mg film coated tablet (EMEA/H/A-29/1411)
(tolperisone)
Applicant /MAH: Meditop Pharmaceutical Co.Ltd.
Rapporteur: Agnes Gyurasics , Co-Rapporteur: Johann Lodewijk Hillege, RMS: HU, CMS: DE, NL, BE, LU, Mutual recognition procedures: HU/H/0373/001-002/MR and HU/H/0377/001-002/MR

Scope: Lack of bioequivalence studies to evaluate the food effect.
List of Questions adopted 22.01.2015.

- Opinion: **For adoption**

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

Haldol and associated names (EMEA/H/A-30/1393) (haloperidol), Janssen-Cilag Group of companies and associated companies
Rapporteur: Martina Weise, Co-Rapporteur: Ivana Mikacic,

Scope: Harmonisation due to large differences in sections 4.1 (age; indications) and 4.2 (special population; general dosing) and in other (non)clinical sections of the SmPC (4.3 – 5.3).

- Request for extension of clock stop to respond to the List of Outstanding Issues adopted in March 2015: **For adoption**

Haldol decanoate and associated names (EMEA/H/A-30/1405) (haloperidol) Janssen-Cilag Group of companies and associated companies
Rapporteur: Martina Weise, Co-Rapporteur: Ivana Mikacic,

Scope: Harmonisation due to large differences in sections 4.1 (age; indications) and 4.2 (special population; general dosing) and in other (non)clinical sections of the SmPC (4.3 – 5.3).

- Request for extension of clock stop to respond to the List of Outstanding Issues adopted in March 2015: **For adoption**

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

Gadolinium containing contrast agents, Gd-Cas (EMEA/H/A-31/1097)
Rapporteur: Rafe Suvarna, Co-Rapporteur: Pieter de Graeff

Responses from the company: **For discussion**

Adrenaline auto injectors (EMEA/H/A-31/1398)
Rapporteur: Alar Irs, Co-Rapporteur: Robert James Hemmings,
Article 31 triggered by the MHRA due to the lack of robust evidence that the devices deliver the adrenaline intramuscularly in all patients. List of Outstanding Issues adopted on 25.09.2014 and 26.02.2015.

- PRAC advice to CHMP: **For information**

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

GVK Biosciences (EMEA/H/A-31/1408)
Re-examination Rapporteur: Hubert Leufkens, re-examination Co-Rapporteur: Karsten Bruins Slot, Article 31 procedure triggered by the European Commission concerning GVK Biosciences Private Limited (GVK Bio), Swarna Jayanthi commercial complex, Ameerpet, Hyderabad 500 038, India following critical GCP deficiencies reported during an inspection performed by the ANSM (Agency for Medicines and Health Products Safety, France) on 19-23 May 2014. Opinion adopted on 22.01.2015.

- Letters of intent: **For information**
- Detailed grounds for the re-examination: **For information**

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

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

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

12.11. 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)

13. Pharmacovigilance issues

Summary of recommendations and advice of PRAC meeting held on 7-10 April 2015: **For information**	
List of Union Reference Dates and frequency of submission of Periodic Safety Update Reports (EURD list) for April 2015: **For adoption**	
Early Notification System: April 2015 Early Notification System on Envisaged CHMP Recommendations for Regulatory Action (based on Identified Safety Concerns) Accompanied by Communication to the General Public: **for information**	

14. Inspections

14.1. GMP inspections

Request for GMP inspections: **For adoption**	*Disclosure of information related to GMP inspections will not be published as it undermines the purpose of such inspections.*

14.2. GCP inspections

Request for GCP inspections: **For adoption**	*Disclosure of information related to GCP inspections will not be published as it undermines the purpose of such inspections.*

14.3. Pharmacovigilance inspections

Request for Pharmacovigilance inspections: **For adoption**	*Disclosure of information related to Pharmacovigilance inspections will not be published as it undermines the purpose of such inspections.*

14.4. GLP inspections

Request for GLP inspections: **For adoption**	*Disclosure of information related to GLP inspections will not be published as it undermines*

	the purpose of such inspections.

15. Innovation Task Force

15.1. Minutes of Innovation Task Force: For information

15.2. Briefing meetings (Innovation Task Force)

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

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

15.4. Nanomedicines activities

16. Scientific Advice Working Party (SAWP)

Report from the SAWP meeting held on 7-10 April 2015. Table of conclusions: **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.*

17. Satellite Groups

17.1. Coordination Group for Mutual Recognition and Decentralised Procedures

Report from the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on the meeting held on 20-22 April 2015: **For information**
CMDh question to CHMP (PKWP, SWP) regarding potential risk of longer half-life of acitretin, • PKWP / SWP position: **For adoption**

18. Other Committees

18.1. Committee for Orphan Medicinal Products (COMP)

Report from the COMP meeting held on 14-16 April 2015: **For information**

18.2. Committee for Herbal Medicinal Products (HMPC)

Report from the HMPC meeting held on 9-12 March 2015: **For information**

18.3. Paediatric Committee (PDCO)

PIPs reaching D30 at April 2015 PDCO: **For information**

Report from the PDCO meeting held on held on 15-17 April 2015: **For information**

18.4. Committee for Advanced Therapies (CAT)

Table of Decisions of CAT meeting held on 16-17 April 2015: **For information**

19. Invented name issues

Table of Decisions of the NRG meeting held in March 2015: **For adoption**

20. Any other business

Proposal for a pre-marketing risk-based model for medicinal product testing – Pilot procedure: **For adoption**

Update on activities related to revised RMP Assessment process in 2015

- Implementation of the revised RMP assessment process: **For discussion**

CHMP representatives at the Pharmacovigilance Implementation Group

- Invitation to an additional CHMP representative to join the Group: **For discussion**

Committees' harmonised agenda template: **For information**	
Proposal for update of the use of conditional Marketing Authorisation • Reflection paper: **For discussion** • Proposal for update of Draft CHMP Guideline on conditional marketing authorisation: **For discussion**	
Revision of the Guideline on clinical development of fixed combination medicinal products: **For adoption for 6-month public consultation**	
Blood Products Working Party Outline for EMA Workshop to be held on 1-2 July 2015 on Haemophilia Registries: **For adoption**	The document will be published on the EMA website.
Letter to DG ENV relating to the non-technical project summaries that companies provide when seeking authorisation for approval of an animal test: **For agreement**	The letter suggests including a cross reference to relevant Ph Eur monograph where relevant
Criteria for competence and experience of Committee members - for recommendation to NCAs in appointment process	
Cardiovascular Working Party Draft Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases (EMA/CHMP/50549/2015): **For adoption for 3 month public consultation**	
Quality Working Party Guideline on Manufacture of the Finished Dosage Form (EMA/CHMP/QWP/BWP/245074): **For adoption for 6-month public consultation** Concept paper on the development of a guideline on quality and equivalence of topical products (EMA/CHMP/QWP/245108/2015): **For information**	
Nomination of Hrefna Gudmundsdóttir (IS) as an observer for the Rheumatology/Immunology Working Party: **For adoption**	

List of participants

List of participants including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 20-23 April 2015 meeting.

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 1)*

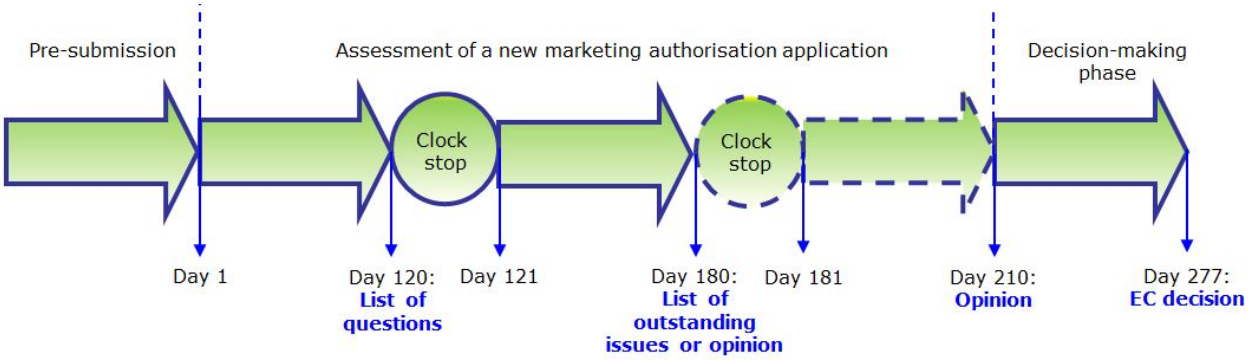
The items listed in this section are those for which marketing authorisation holders (MAHs) or applicants have been invited to the CHMP plenary meeting to address questions raised by the Committee. Oral explanations normally relate to on-going applications (section 2 and 3) or referral procedures (section 12) but can relate to any other issue for which the CHMP would like to discuss with company representatives in person.

New applications *(section 2)*

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

Section 2.1 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 2.2 (**Day 180 List of outstanding issues**) and 2.3 (**Day 120 list of questions**).

CHMP discussions may also occur at any other stage of the evaluation, and these are listed under section 2.4, **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 2.5, **products in the decision making phase**.

Extension of marketing authorisations according to Annex I of Reg. 1234/2008 *(section 3)*

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 4)*

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 3. 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 5)*

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 6)*

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

Re-examination procedures *(section 7)*

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 8)*

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 9)*

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 10)*

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 11)*

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 12)*

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 13)*

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 14)*

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 15)*

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 16)*

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 17)*

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 18)*

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.