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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for medicinal products for human use (CHMP) Minutes of the meeting on 23-26 April 2018

Chair: Tomas Salmonson – Vice-Chair: Harald Enzmann

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. 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 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 minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).



Table of contents

1.	Introduction	8
1.1.	Welcome and declarations of interest of members, alternates and experts.....	8
1.2.	Adoption of agenda	8
1.3.	Adoption of the minutes	8
2.	Oral Explanations	9
2.1.	Pre-authorisation procedure oral explanations.....	9
2.1.1.	erenumab - EMEA/H/C/004447	9
2.1.2.	paclitaxel - Orphan - EMEA/H/C/004154.....	9
2.1.3.	eteplirsen - Orphan - EMEA/H/C/004355	9
2.1.4.	adalimumab - EMEA/H/C/004866	10
2.1.5.	adalimumab - EMEA/H/C/004865	10
2.1.6.	adalimumab - EMEA/H/C/004320	10
2.1.7.	vestronidase alfa - Orphan - EMEA/H/C/004438	10
2.1.8.	nitisinone - EMEA/H/C/004582	11
2.1.9.	Restaysis - ciclosporin - EMEA/H/C/004229.....	11
2.2.	Re-examination procedure oral explanations	11
2.3.	Post-authorisation procedure oral explanations	11
2.4.	Referral procedure oral explanations	11
3.	Initial applications	12
3.1.	Initial applications; Opinions.....	12
3.1.1.	Alsitek - masitinib - Orphan - EMEA/H/C/004398.....	12
3.1.2.	Biktarvy - bictegravir / emtricitabine / tenofovir alafenamide - EMEA/H/C/004449.....	12
3.1.3.	Carmustine Obvius - carmustine - EMEA/H/C/004326	13
3.1.4.	Dzuevo - sufentanil - EMEA/H/C/004335	13
3.2.	Initial applications; List of outstanding issues (Day 180; Day 120 for procedures with accelerated assessment timetable)	14
3.2.1.	erenumab - EMEA/H/C/004447	14
3.2.2.	paclitaxel - Orphan - EMEA/H/C/004154.....	14
3.2.3.	lesinurad / allopurinol - EMEA/H/C/004412	14
3.2.4.	adalimumab - EMEA/H/C/004866	15
3.2.5.	adalimumab - EMEA/H/C/004865	15
3.2.6.	adalimumab - EMEA/H/C/004429	15
3.2.7.	adalimumab - EMEA/H/C/004320	16
3.2.8.	vigabatrin - PUMA - EMEA/H/C/004534	16
3.2.9.	vestronidase alfa - Orphan - EMEA/H/C/004438	16
3.2.10.	nitisinone - EMEA/H/C/004582	17

3.2.11.	naldemedine - EMEA/H/C/004256.....	17
3.2.12.	inotersen - Orphan - EMEA/H/C/004782	18
3.2.13.	trastuzumab - EMEA/H/C/004463	18
3.2.14.	abemaciclib - EMEA/H/C/004302	18
3.2.15.	daunorubicin / cytarabine - Orphan - EMEA/H/C/004282	19
3.2.16.	volanesorsen - Orphan - EMEA/H/C/004538.....	19
3.2.17.	axicabtagene ciloleucel - Orphan - ATMP - EMEA/H/C/004480	19
3.3.	Initial applications; List of questions (Day 120; Day 90 for procedures with accelerated assessment timetable)	20
3.3.1.	avacopan - Orphan - EMEA/H/C/004487	20
3.3.2.	zanamivir - EMEA/H/C/004102	20
3.3.3.	romosozumab - EMEA/H/C/004465.....	20
3.3.4.	fexinidazole - Article 58 - EMEA/H/W/002320.....	20
3.3.5.	tisagenlecleucel - Orphan - ATMP - EMEA/H/C/004090	21
3.3.6.	patisiran - Orphan - EMEA/H/C/004699	21
3.4.	Update on on-going initial applications for Centralised procedure.....	21
3.4.1.	dengue tetravalent vaccine (live, attenuated) - EMEA/H/C/004171	21
3.4.2.	adalimumab - EMEA/H/C/004475	22
3.4.3.	botulinum toxin type A - EMEA/H/C/004587.....	22
3.5.	Re-examination of initial application procedures under Article 9(2) of Regulation no 726/2004	22
3.5.1.	Alsitek - masitinib - Orphan - EMEA/H/C/004398.....	22
3.5.2.	Dexxience - betrixaban - EMEA/H/C/004309	22
3.5.3.	Eladynos - abaloparatide - EMEA/H/C/004157	23
3.5.4.	Nerlynx - neratinib - EMEA/H/C/004030	23
3.6.	Initial applications in the decision-making phase.....	23
3.7.	Withdrawals of initial marketing authorisation application	24
3.7.1.	Prohippur - sodium benzoate - Orphan - EMEA/H/C/004150.....	24
3.7.2.	Restaysis - ciclosporin - EMEA/H/C/004229.....	24

4. Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008 24

4.1.	Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Opinion	24
4.1.1.	Imbruvica - ibrutinib - Orphan - EMEA/H/C/003791/X/0037.....	24
4.1.2.	Sprycel - dasatinib - EMEA/H/C/000709/X/0056/G	25
4.2.	Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Day 180 list of outstanding issues	26
4.2.1.	Bydureon - exenatide - EMEA/H/C/002020/X/0048/G	26
4.3.	Extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008; Day 120 List of question	26

4.4.	Update on on-going extension application according to Annex I of Commission Regulation (EC) No 1234/2008	26
4.5.	Re-examination procedure of extension of marketing authorisation according to Annex I of Commission Regulation (EC) No 1234/2008	26

5. Type II variations - variation of therapeutic indication procedure according to Annex I of Commission Regulation (EC) No 1234/2008 27

5.1.	Type II variations - variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008; Opinions or Requests for supplementary information.....	27
5.1.1.	Blinicyto - blinatumomab - Orphan - EMEA/H/C/003731/II/0011	27
5.1.2.	Cimzia - certolizumab pegol - EMEA/H/C/001037/II/0065.....	27
5.1.3.	Dexdor - dexmedetomidine - EMEA/H/C/002268/II/0026	28
5.1.4.	Jinarc - tolvaptan - EMEA/H/C/002788/II/0009	28
5.1.5.	Keytruda - pembrolizumab - EMEA/H/C/003820/II/0042	29
5.1.6.	Opdivo - nivolumab - EMEA/H/C/003985/II/0039	29
5.1.7.	Opdivo - nivolumab - EMEA/H/C/003985/II/0041	30
5.1.8.	Perjeta - pertuzumab - EMEA/H/C/002547/II/0034.....	30
5.1.9.	Prolia - denosumab - EMEA/H/C/001120/II/0068.....	31
5.1.10.	Rapamune - sirolimus - EMEA/H/C/000273/II/0164	31
5.1.11.	Tagrisso - osimertinib - EMEA/H/C/004124/II/0019	32
5.1.12.	Translarna - ataluren - Orphan - EMEA/H/C/002720/II/0037.....	32
5.1.13.	Venclyxto - venetoclax - Orphan - EMEA/H/C/004106/II/0008	33
5.1.14.	Xeljanz - tofacitinib - EMEA/H/C/004214/II/0006.....	33
5.1.15.	Xultophy - insulin degludec / liraglutide - EMEA/H/C/002647/II/0023.....	34
5.1.16.	Yervoy - ipilimumab - EMEA/H/C/002213/II/0055.....	34
5.2.	Update on on-going Type II variation; variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008	35
5.2.1.	Darzalex - daratumumab - Orphan - EMEA/H/C/004077/II/0011	35
5.3.	Re-examination of Type II variation; variation of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008	35

6. Ancillary medicinal substances in medical devices 35

6.1.	Ancillary medicinal substances in medical devices; Opinions/ Day 180 list of outstanding issues / Day 120 list of questions	35
6.2.	Update of Ancillary medicinal substances in medical devices	35
6.2.1.	human fibrinogen / human thrombin - EMEA/H/D/004308	35

7. Procedure under Article 83(1) of Regulation (EC) 726/2004 (Compassionate Use) 36

7.1.	Procedure under Article 83(1) of Regulation (EC) 726/2004 (Compassionate Use)	36
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8.	Pre-submission issues	36
8.1.	Pre-submission issue	36
8.2.	Priority Medicines (PRIME)	36
8.2.1.	List of applications received	36
8.2.2.	Recommendation for PRIME eligibility.....	36
9.	Post-authorisation issues	37
9.1.	Post-authorisation issues	37
9.1.1.	Flixabi - infliximab - EMEA/H/C/004020/MEA 007.1.....	37
9.1.2.	Keytruda - pembrolizumab - EMEA/H/C/003820/ANX/018	37
9.1.3.	Xagrid - anagrelide - EMEA/H/C/00480/S/0081	37
9.1.4.	Zinbryta - daclizumab - EMEA/H/C/003862.....	38
9.1.5.	Tecentriq – atezolizumab - EMEA/H/C/004143	38
10.	Referral procedures	38
10.1.	Procedure for Centrally Authorised products under Article 20 of Regulation (EC) No 726/2004	38
10.2.	Requests for CHMP Opinion under Article 5(3) of Regulation (EC) No 726/2004 ..	38
10.2.1.	Gentamicin – EMEA/H/A-5(3)/1468.....	38
10.3.	Procedure under Articles 5(2) and 10 of Regulation (EC) No 726/2004	39
10.4.	Disagreement between Member States on application for medicinal product (potential serious risk to public health) –under Article 29(4) of Directive 2001/83/EC	39
10.4.1.	Diclofenac Sodium Spray Gel 4% cutaneous spray, solution and associated names– EMEA/H/A-29(4)/1467.....	39
10.4.2.	Paclitaxel Hetero - EMEA/H/A-29(4)/1256.....	40
10.5.	Harmonisation - Referral procedure under Article 30 of Directive 2001/83/EC....	40
10.6.	Community Interests - Referral under Article 31 of Directive 2001/83/EC	40
10.7.	Re-examination Procedure under Article 32(4) of Directive 2001/83/EC.....	40
10.8.	Procedure under Article 107(2) of Directive 2001/83/EC	41
10.9.	Disagreement between Member States on Type II variation– Arbitration procedure initiated by MAH under Article 6(13) of Commission Regulation (EC) No 1084/2003	41
10.10.	Procedure under Article 29 of Regulation (EC) 1901/2006.....	41
10.11.	Referral under Article 13 Disagreement between Member States on Type II variation– Arbitration procedure initiated by Member State under Article 13 (EC) of Commission Regulation No 1234/2008	41
11.	Pharmacovigilance issue	41
11.1.	Early Notification System	41
12.	Inspections	41
12.1.	GMP inspections	41

12.2.	GCP inspections	41
12.3.	Pharmacovigilance inspections	41
12.4.	GLP inspections	42
13.	Innovation Task Force	42
13.1.	Minutes of Innovation Task Force	42
13.2.	Innovation Task Force briefing meetings	42
13.2.1.	ITF briefing meeting.....	42
13.3.	Requests for CHMP Opinion under Article 57(1)J and (1)P of Regulation (EC) No 726/2004	42
13.4.	Nanomedicines activities	42
14.	Organisational, regulatory and methodological matters	42
14.1.	Mandate and organisation of the CHMP	42
14.1.1.	Enhanced early dialogue to facilitate accelerated assessment of priority medicines (PRIME) – revision 1	42
14.2.	Coordination with EMA Scientific Committees	43
14.2.1.	Pharmacovigilance Risk Assessment Committee (PRAC)	43
14.2.2.	Committee for Advanced Therapies (CAT)	43
14.2.3.	Committee for Herbal Medicinal Products (HMPC)	43
14.2.4.	Paediatric Committee (PDCO).....	43
14.2.5.	Committee for Orphan Medicinal Products (COMP)	44
14.2.6.	Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)	44
14.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	44
14.3.1.	Scientific Advice Working Party (SAWP)	44
14.3.2.	Biologics Working Party (BWP)	44
14.3.3.	Biostatistics Working Party (BSWP)	45
14.3.4.	Blood Products Working Party (BPWP)	45
14.3.5.	Cardiovascular Working Party (CVSWP)	45
14.3.6.	Rheumatology/Immunology Working Party (RIWP)	45
14.3.7.	Safety Working Party (SWP)	46
14.3.8.	Modelling and Simulation Working Group (MSWG)	46
14.3.9.	Ad-hoc Influenza Working Group	46
14.3.10.	Pharmacogenomics Working Party (PGWP)	47
14.3.11.	Temporary working parties and drafting groups composition	47
14.3.12.	The Active Substance Master File Working Group (ASMF WG).....	47
14.4.	Cooperation within the EU regulatory network	47
14.5.	Cooperation with International Regulators	47
14.5.1.	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – EMA/CHMP representation.....	47

14.6.	Contacts of the CHMP with external parties and interaction with the Interested Parties to the Committee	47
14.7.	CHMP work plan	47
14.8.	Planning and reporting	48
14.9.	Others	48
15.	Any other business	48
15.1.	AOB topic	48
15.1.1.	Preparedness of the system and capacity increase	48
15.1.2.	Update on EMA relocation	48
15.1.3.	Article 58: Update from the March 2017 'Malta' CHMP meeting with African regulators	48
15.1.4.	Information on the legislative proposal for HTA collaboration	48
16.	List of participants	49
17.	Explanatory notes	53

1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the list of participants and restrictions. See (current) April 2018 CHMP minutes for the list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the CHMP plenary session held 23-26 April 2018 (to be published post May 2018 CHMP meeting).

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

CHMP agenda for 23-26 April 2018

The CHMP adopted the agenda.

1.3. Adoption of the minutes

CHMP minutes for 19-22 March 2018

The CHMP adopted the CHMP minutes for 19-22 March 2018. The Minutes of the April 2018 CHMP ORGAM meeting held on 16 April 2018, together with all decisions taken at that meeting, were adopted.

2. Oral Explanations

2.1. Pre-authorisation procedure oral explanations

2.1.1. erenumab - EMEA/H/C/004447

indicated for prophylaxis of migraine in adults

Scope: Oral explanation

Action: Oral explanation to be held on 24 April 2018 at time 11.00

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 12.10.2017.

See 3.2

An oral explanation was held on 24 April 2018 at time 11.00, focusing on the posology of the product.

2.1.2. paclitaxel - Orphan - EMEA/H/C/004154

Oasmia Pharmaceutical AB; treatment of ovarian cancer

Scope: Oral explanation

Action: Oral explanation to be held on 24 April 2018 at time 09.00

List of Outstanding Issues adopted on 14.09.2017, 18.05.2017. List of Questions adopted on 23.06.2016.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.3. eteplirsen - Orphan - EMEA/H/C/004355

AVI Biopharma International Ltd; treatment of Duchenne muscular dystrophy

Scope: Oral explanation

Action: Oral explanation to be held on 24 April 2018 at time 14.00

List of Outstanding Issues adopted on 14.12.2017. List of Questions adopted on 21.04.2017.

Participation of patient representatives

An oral explanation was held on 24 April 2018 at time 14.30.

2.1.4. adalimumab - EMEA/H/C/004866

treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

Scope: Oral explanation

Action: Oral explanation to be held on 25 April 2018 at time 11.00

List of Outstanding Issues adopted on 22.02.2018.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.5. adalimumab - EMEA/H/C/004865

treatment of juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), uveitis, paediatric uveitis

Scope: Oral explanation

Action: Oral explanation to be held on 25 April 2018 at time 11.00

List of Outstanding Issues adopted on 22.02.2018.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.6. adalimumab - EMEA/H/C/004320

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

Scope: Oral explanation

Action: Oral explanation to be held 25 April 2018 at time 11.00

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 14.09.2017.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.7. vestronidase alfa - Orphan - EMEA/H/C/004438

Ultragenyx Germany GmbH indicated for the treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages

Scope: Oral explanation

Action: Oral explanation to be held on 24 April 2018 at time 16.00

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 14.09.2017.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.8. nitisinone - EMEA/H/C/004582

treatment of hereditary tyrosinemia type 1

Scope: Oral explanation

Action: Oral explanation to be held on 25 April 2018 at time 09.00

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 22.06.2017.

The CHMP agreed that no oral explanation was needed at this time.

See 3.2

2.1.9. Restasis - ciclosporin - EMEA/H/C/004229

Allergan Pharmaceuticals International Ltd; for the treatment of moderate dry eye disease in adults

Scope: Oral explanation, the draft list of experts for the ad hoc expert group meeting adopted by written procedure on 11 April 2018, report from ad-hoc expert group held on 13 April 2018.

Action: Oral explanation to be held on 25 April 2018 at time 14.00

List of Outstanding Issues adopted on 22.02.2018, 14.09.2017. List of Questions adopted on 23.03.2017.

The CHMP considered that an oral explanation was not needed.

The CHMP noted the withdrawal of initial marketing authorisation application.

See 3.7

2.2. Re-examination procedure oral explanations

No items

2.3. Post-authorisation procedure oral explanations

No items

2.4. Referral procedure oral explanations

No items

3. Initial applications

3.1. Initial applications; Opinions

3.1.1. Alsitek - masitinib - Orphan - EMEA/H/C/004398

AB Science; treatment of amyotrophic lateral sclerosis

Scope: Opinion adopted by written procedure on 18 April 2018

Action: For information

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

List of Outstanding Issues adopted on 12.10.2017. List of Questions adopted on 26.01.2017.

The CHMP adopted a negative opinion by consensus via written procedure on 18 April 2018, recommending the refusal of the marketing authorisation application. The CHMP adopted the assessment report.

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

The refusal question and answers document was circulated for information.

See 3.5

3.1.2. Biktarvy - bictegravir / emtricitabine / tenofovir alafenamide - EMEA/H/C/004449

Gilead Sciences International Limited; treatment of adults infected with human immunodeficiency virus-1 (HIV-1)

Scope: Opinion

Action: For adoption

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

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 09.11.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion recommending the granting of a marketing authorisation by consensus together with the CHMP assessment report and translation timetable.

Furthermore, the CHMP considered that bictegravir is a new active substance, as claimed by the applicant.

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

The legal status was agreed as medicinal product subject to restricted medical prescription.

The summary of opinion was circulated for information.

3.1.3. Carmustine Obvius - carmustine - EMEA/H/C/004326

Obvius Investment B.V; treatment of brain tumors, multiple myeloma, Hodgkin's disease and non-Hodgkin's lymphomas

Scope: Opinion

Action: For adoption

Generic application (Article 10(1) of Directive No 2001/83/EC)

List of Outstanding Issues adopted on 22.02.2018, 12.10.2017, 20.07.2017. List of Questions adopted on 13.10.2016.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion recommending the granting of a marketing authorisation by consensus together with the CHMP assessment report and translation timetable.

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

The legal status was agreed as medicinal product subject to restricted medical prescription.

The summary of opinion was circulated for information.

The CHMP adopted the similarity assessment report for Carmustine Obvius.

3.1.4. Dzuveo - sufentanil - EMEA/H/C/004335

FGK Representative Service GmbH; management of acute moderate to severe pain

Scope: Opinion

Action: For adoption

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

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 20.07.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion recommending the granting of a marketing authorisation by consensus together with the CHMP assessment report and translation timetable.

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

The legal status was agreed as medicinal product subject to special and restricted medical prescription.

The summary of opinion was circulated for information.

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

3.2.1. erenumab - EMEA/H/C/004447

indicated for prophylaxis of migraine in adults

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 12.10.2017.

See 2.1

An oral explanation was held on 24 April 2018 at time 11.00, focusing on the posology of the product.

The Committee discussed the treatment failure population and data presented during the OE.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

3.2.2. paclitaxel - Orphan - EMEA/H/C/004154

Oasmia Pharmaceutical AB; treatment of ovarian cancer

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 14.09.2017, 18.05.2017. List of Questions adopted on 23.06.2016.

See 2.1

The CHMP agreed that no oral explanation was needed at this time.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 3rd list of outstanding issues with a specific timetable.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the 3rd list of outstanding issues with a specific timetable.

3.2.3. lesinurad / allopurinol - EMEA/H/C/004412

gout

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 09.11.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.4. adalimumab - EMEA/H/C/004866

treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis, paediatric uveitis

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018.

See 2.1

The CHMP agreed that no oral explanation was needed at this time.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

3.2.5. adalimumab - EMEA/H/C/004865

treatment of juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), uveitis, paediatric uveitis

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018.

See 2.1

The CHMP agreed that no oral explanation was needed at this time.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

3.2.6. adalimumab - EMEA/H/C/004429

treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 14.09.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues

The Committee adopted a list of outstanding issues.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the list of outstanding issues with a specific timetable.

3.2.7. [adalimumab - EMEA/H/C/004320](#)

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

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 14.09.2017.

See 2.1

The CHMP agreed that no oral explanation was needed at this time.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

3.2.8. [vigabatrin - PUMA - EMEA/H/C/004534](#)

treatment in monotherapy of infantile spasms (West's syndrome) and resistant partial epilepsy in infants and children

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 14.12.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.9. [vestronidase alfa - Orphan - EMEA/H/C/004438](#)

Ultragenyx Germany GmbH indicated for the treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 14.09.2017.

See 2.1

The CHMP agreed that no oral explanation was needed at this time.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

The CHMP agreed to consult an ad-hoc expert group and adopted a list of questions to this group.

3.2.10. nitisinone - EMEA/H/C/004582

treatment of hereditary tyrosinemia type 1

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 22.06.2017.

See 2.1

The Committee was reminded of the status of this application and its remaining outstanding issues.

The CHMP agreed that no oral explanation was needed at this time.

The Committee adopted a 2nd list of outstanding issues with a specific timetable.

The CHMP agreed to consult the PKWP and adopted a list of questions to this group.

3.2.11. naldemedine - EMEA/H/C/004256

treatment of opioid-induced constipation (OIC) in adult patients.

Scope: List of outstanding issue

Request by the applicant dated 25 April 2018 for an extension of clock stop to respond to the List of outstanding issues adopted in April 2018

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 20.07.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a 2nd list of outstanding issues.

The CHMP agreed to the request by the applicant for an extension to the clockstop to respond to the list of outstanding issues with a specific timetable.

3.2.12. inotersen - Orphan - EMEA/H/C/004782

Accelerated assessment

IONIS USA Ltd; treatment of transthyretin amyloidosis (hATTR)

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 20.02.2018.

The Committee was reminded of the status of this application and its remaining outstanding issues

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.13. trastuzumab - EMEA/H/C/004463

treatment of metastatic and early breast cancer and metastatic gastric cancer (MGC)

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 09.11.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.14. abemaciclib - EMEA/H/C/004302

treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 14.12.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.15. daunorubicin / cytarabine - Orphan - EMEA/H/C/004282

Accelerated assessment

Jazz Pharmaceuticals Ireland Limited; treatment of adults with high-risk acute myeloid leukaemia (AML)

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 20.02.2018.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a list of outstanding issues with a specific timetable.

3.2.16. volanesorsen - Orphan - EMEA/H/C/004538

Akcea Therapeutics UK Ltd.; indicated as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome (FCS)

Scope: List of outstanding issue

Action: For adoption

List of Questions adopted on 14.12.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues.

The Committee adopted a list of outstanding issues with a specific timetable.

The CHMP agreed to consult an ad-hoc expert group and adopted a list of questions to this group.

3.2.17. axicabtagene ciloleucel - Orphan - ATMP - EMEA/H/C/004480

Kite Pharma EU B.V.; treatment of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL)

Scope: List of outstanding issue

Action: For adoption

List of Outstanding Issues adopted on 20.04.2018. List of Questions adopted on 08.12.2017.

The Committee was reminded of the status of this application and its remaining outstanding issues. The CHMP was updated on discussions at the CAT during their April 2018 meeting.

The Committee adopted a 2nd list of outstanding issues with amendments together with a specific timetable.

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

3.3.1. avacopan - Orphan - EMEA/H/C/004487

ChemoCentryx Ltd; induction of response in adult patients with granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA)

Scope: List of questions

Action: For adoption

The Committee discussed the issues identified in this application

The Committee adopted the CHMP recommendation and scientific discussion together with the list of questions.

The CHMP agreed to the request by the applicant for an extension to the clock stop to respond to the list of questions.

3.3.2. zanamivir - EMEA/H/C/004102

treatment of influenza A or B virus infection

Scope: List of questions

Action: For adoption

The Committee discussed the issues identified in this application

The Committee adopted the CHMP recommendation and scientific discussion together with the list of questions.

3.3.3. romosozumab - EMEA/H/C/004465

Treatment of osteoporosis

Scope: List of questions

Action: For adoption

The Committee discussed the issues identified in this application.

The Committee adopted the CHMP recommendation and scientific discussion together with the list of questions.

3.3.4. fexinidazole - Article 58 - EMEA/H/W/002320

Accelerated assessment

treatment of human African trypanosomiasis (HAT)

Scope: List of questions

Action: For adoption

The Committee discussed the issues identified in this application.

The Committee adopted the CHMP recommendation and scientific discussion together with the list of questions.

3.3.5. [tisagenlecleucel - Orphan - ATMP - EMEA/H/C/004090](#)

Accelerated assessment

Novartis Europharm Limited; treatment of B cell acute lymphoblastic leukaemia (ALL) and diffuse large B cell lymphoma (DLBCL)

Scope: Revised list of questions

Action: For adoption

List of questions adopted on 16.03.2018.

The Committee discussed the issues identified in this application. The CHMP was updated on discussions at the CAT during their April 2018 meeting.

The Committee adopted the revised CHMP recommendation and scientific discussion together with the revised list of questions with amendments.

3.3.6. [patisiran - Orphan - EMEA/H/C/004699](#)

Accelerated assessment

Alnylam UK Limited; treatment of hereditary transthyretin-mediated amyloidosis

Scope: List of questions

Action: For adoption

The Committee discussed the issues identified in this application.

The Committee adopted the CHMP recommendation and scientific discussion together with the list of questions.

3.4. [Update on on-going initial applications for Centralised procedure](#)

3.4.1. [dengue tetravalent vaccine \(live, attenuated\) - EMEA/H/C/004171](#)

indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4

Scope: SAG list of questions and list of experts for the SAG vaccines meeting on 30 April 2018

Action: For adoption

List of Outstanding Issues adopted on 23.03.2017. List of Questions adopted on 21.07.2016.

The CHMP adopted the list of questions and list of experts to the SAG vaccines meeting on 30 April 2018.

3.4.2. adalimumab - EMEA/H/C/004475

treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

Scope: Request by the applicant dated 6 April 2018 for an extension of clock stop to respond to the List of Questions adopted in March 2018

Action: For adoption

List of Questions adopted on 23.03.2018.

The CHMP agreed to the request by the applicant for an extension of clock stop to respond to the List of Questions adopted in March 2018.

3.4.3. botulinum toxin type A - EMEA/H/C/004587

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

Scope: Request for an extension of clock stop to respond to the List of Questions adopted in November 2017

Action: For adoption

The CHMP agreed to the request by the applicant for an extension of clock stop to respond to the List of Questions adopted in November 2017

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

3.5.1. Alsitek - masitinib - Orphan - EMEA/H/C/004398

AB Science; treatment of amyotrophic lateral sclerosis

Scope: Appointment of re-examination rapporteurs, draft timetable, SAG involvement

Action: For discussion

Opinion adopted on 18.04.2018.

Letter from the applicant dated 24 April 2018 requesting a re-examination of the Opinion adopted on 18 April 2018

The CHMP appointed a re-examination Rapporteur and a re-examination Co-Rapporteur.

The CHMP noted the draft timetable.

See 3.1

3.5.2. Dexxience - betrixaban - EMEA/H/C/004309

Portola Pharma UK Limited; treatment of prophylaxis of venous thromboembolism (VTE)

Scope: Appointment of re-examination rapporteurs, draft timetable, SAG involvement

Action: For discussion

Opinion adopted on 22.03.2018.

Letter from the applicant dated 9 April 2018 requesting a re-examination of the Opinion adopted on 22 March 2018.

The CHMP appointed a re-examination Rapporteur and a re-examination Co-Rapporteur.

The CHMP noted the draft timetable.

3.5.3. [Eladynos - abaloparatide - EMEA/H/C/004157](#)

Radius International Ltd; treatment of osteoporosis

Scope: Appointment of re-examination rapporteurs, draft timetable

Action: For discussion

Opinion adopted on 22.03.2018.

Letter from the applicant dated 6 April 2018 requesting a re-examination of the Opinion adopted on 22 March 2018.

The CHMP appointed a re-examination Rapporteur and a re-examination Co-Rapporteur.

The CHMP noted the draft timetable.

3.5.4. [Nerlynx - neratinib - EMEA/H/C/004030](#)

Puma Biotechnology Limited; extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy

Scope: Draft re-examination timetable

Action: For information

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

Opinion adopted on 22 February 2018, Oral explanation held on 23.01.2018. List of Outstanding Issues adopted on 20.07.2017. List of Questions adopted on 15.12.2016.

The CHMP noted the draft re-examination timetable.

3.6. [Initial applications in the decision-making phase](#)

No items

3.7. Withdrawals of initial marketing authorisation application

3.7.1. Prohippur - sodium benzoate - Orphan - EMEA/H/C/004150

Lucane Pharma; treatment of non ketotic hyperglycinemia, urea cycle disorders including carbamoyl-phosphate synthase-1 deficiency, ornithine transcarbamylase deficiency, citrullinaemia type 1, argininosuccinic aciduria, hyperargininaemia, n-acetylglutamate synthase deficiency, ornithine translocase deficiency and lysinuric protein intolerance

Scope: Withdrawal of initial marketing authorisation application

Action: For information

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 22.06.2017.

The CHMP noted the withdrawal of initial marketing authorisation application.

3.7.2. Restasis - ciclosporin - EMEA/H/C/004229

Allergan Pharmaceuticals International Ltd; for the treatment of moderate dry eye disease in adults

Scope: Withdrawal of initial marketing authorisation application

Action: For information

List of Outstanding Issues adopted on 22.02.2018, 14.09.2017. List of Questions adopted on 23.03.2017.

The CHMP noted the withdrawal 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. Imbruvica - ibrutinib - Orphan - EMEA/H/C/003791/X/0037

Janssen-Cilag International NV

Rapporteur: Filip Josephson, PRAC Rapporteur: Patrick Batty

Scope: "Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths (140 mg, 280 mg, 420 mg and 560 mg)."

Action: For adoption

List of Questions adopted on 22.02.2018.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The CHMP adopted the similarity assessment report for Imbruvica

4.1.2. [Sprycel - dasatinib - EMEA/H/C/000709/X/0056/G](#)

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Sinan B. Sarac, Co-Rapporteur: Fátima Ventura, PRAC Rapporteur: Doris Stenver

Scope:

"1. Extension application to introduce a new pharmaceutical form (powder for oral suspension) associated with a new strength (10 mg/ml) indicated in the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML CP), or with Ph+ CML CP resistant or intolerant to prior therapy including imatinib.

2. C.1.6.a (type II) To include the treatment of paediatric patients with newly diagnosed Ph+ CML in chronic phase (Ph+ CML CP) or Ph+ CML CP resistant or intolerant to prior therapy including imatinib for Sprycel film-coated tablets. Sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, to add a warning on effects on growth and development in the paediatric population and to update the safety information.

Annex A, Annex II, Labelling, The Package Leaflet and the RMP (version 15.2) are updated in accordance."

Action: For adoption

List of Outstanding Issues adopted on 22.02.2018. List of Questions adopted on 14.09.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The CHMP adopted the similarity assessment report for Sprycel

The CHMP noted the letter of recommendation dated 16 April 2018.

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

4.2.1. **Bydureon - exenatide - EMEA/H/C/002020/X/0048/G**

AstraZeneca AB

Rapporteur: Kristina Dunder, PRAC Rapporteur: Qun-Ying Yue

Scope: "Extension application to introduce new pharmaceutical form (prolonged-release suspension for injection) grouped with type II variation to align the PI for the approved Bydureon products (powder and solvent for prolonged-release suspension for injection, and powder and solvent for prolonged-release suspension for injection in pre-filled pen) with the PI proposed for the Bydureon new pharmaceutical form (prolonged-release suspension for injection in autoinjector). In addition, the MAH took the opportunity to make minor editorial changes through SmPC. Moreover, RMP version 28 has been submitted as part of this application."

Action: For adoption

List of Questions adopted on 25.01.2018.

The Committee discussed the issues identified in this application. It was noted that responses are expected to remaining questions, which are related to the quality.

The Committee adopted the CHMP recommendation and scientific discussion together with the list of outstanding issues and a specific timetable.

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

No items

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

No items

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

No items

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

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

5.1.1. Blincyto - blinatumomab - Orphan - EMEA/H/C/003731/II/0011

Amgen Europe B.V.

Rapporteur: Alexandre Moreau, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Eva Jirsová

Scope: "Extension of Indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and to update the safety information. The Labelling is updated in accordance.

RMP version 4.0 is included in this submission."

Action: For adoption

Request for Supplementary Information adopted on 14.12.2017, 22.06.2017.

The Committee discussed the issues identified in this application. The members discussed the clinical data and identified uncertainties on the long-term efficacy and safety of the product in the proposed extension of indication.

The Committee adopted a 3rd request for supplementary information with a specific timetable.

5.1.2. Cimzia - certolizumab pegol - EMEA/H/C/001037/II/0065

UCB Pharma S.A.

Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga

Scope: "Extension of Indication to include plaque psoriasis in adult patients for Cimzia; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 13 has also been submitted."

Action: For adoption

Request for Supplementary Information adopted on 22.03.2018, 09.11.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP

recommendations.

The summary of opinion was circulated for information.

5.1.3. [Dexdor - dexmedetomidine - EMEA/H/C/002268/II/0026](#)

Orion Corporation

Rapporteur: Greg Markey, Co-Rapporteur: Filip Josephson, PRAC Rapporteur: Julie Williams

Scope: "Extension of Indication to include "For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation" for Dexdor; as a consequence, section 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

RMP version 7 has been submitted"

Action: For adoption

The Committee discussed the issues identified in this application, mainly relating to the posology and the efficacy data.

The Committee adopted a request for supplementary information with a specific timetable.

5.1.4. [Jinarc - tolvaptan - EMEA/H/C/002788/II/0009](#)

Otsuka Pharmaceutical Europe Ltd

Rapporteur: Greg Markey, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Julie Williams

Scope: "Extension of Indications based on the results of a completed Post Authorisation Efficacy Study (PAES, Trial 156-13-210) as mandated by Annex II of the Product Information with tolvaptan (ANX 006). Trial 156-13-210 is a Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease.

Updates to SmPC Sections 4.1, 4.8 (to add 'abdominal pain' to the table of adverse events and present the data in line with QRD recommendations) and 5.1 are being proposed. The Package Leaflet is updated in accordance. Minor additional editorial changes to the PI were also carried out.

Version 13.2 of the RMP was submitted, updated to reflect the study results."

Action: For adoption

The Committee discussed the issues identified in this application, mainly relating to updates of the SmPC and RMP.

The Committee adopted a request for supplementary information with a specific timetable.

5.1.5. Keytruda - pembrolizumab - EMEA/H/C/003820/II/0042

Merck Sharp & Dohme Limited

Rapporteur: Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Sabine Straus

Scope: "Extension of Indication to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012/ KEYNOTE-055). KN040 is a randomized, multi-center, pivotal phase III study investigating KEYTRUDA as a monotherapy versus standard treatment (methotrexate, docetaxel or cetuximab) in 495 patients with recurrent or metastatic HNSCC who have previously progressed on prior platinum. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include in SmPC section 5.2 the description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure.

An updated RMP version 15.1 was provided as part of the application."

Action: For adoption

The Committee discussed the issues identified in this application. It was noted that the positive benefit-risk in CPS < 1 should be justified, or restricted the indication to subjects with CPS ≥ 1. There were also questions raised regarding the methodology of the study and statistical significance.

The Committee adopted a request for supplementary information with a specific timetable.

5.1.6. Opdivo - nivolumab - EMEA/H/C/003985/II/0039

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: "Extension of Indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. The RMP version version 11.0 has also been submitted."

Action: For adoption

Request for Supplementary Information adopted on 14.12.2017.

The Committee discussed the issues identified in this application. The main uncertainties raised were related to clinical aspects - the B/R for the to-be-treated EU patient population cannot be assessed due to the uncertainties regarding extrapolation of data from Asian to EU patients.

The Committee adopted a request for supplementary information with a specific timetable.

5.1.7. Opdivo - nivolumab - EMEA/H/C/003985/II/0041

Bristol-Myers Squibb Pharma EEIG

Co-Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: "Extension of Indication to include adjuvant treatment of adults and adolescents 12 years of age and older with completely resected Stage III and IV melanoma for OPDIVO; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from the pivotal Study CA209238. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the PI.

The RMP version 12.0 has also been submitted. The MAH also took the opportunity to revise the due dates for two Category 4 studies (CA209172 and CA209171) to a later date."

Action: For adoption

Request for Supplementary Information adopted on 25.01.2018.

The Committee discussed the issues identified in this application. The remaining issues related to clinical efficacy and safety questions were noted.

The Committee adopted a request for supplementary information with a specific timetable.

The CHMP agreed to consult a SAG and adopted a list of questions to this group.

5.1.8. Perjeta - pertuzumab - EMEA/H/C/002547/II/0034

Roche Registration GmbH

Rapporteur: Sinan B. Sarac, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Doris Stenver

Scope: "Extension of Indication for Perjeta in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive early breast cancer. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase III study BIG-4-11/BO25126/TOC4939g (APHINITY). With the submission of the APHINITY data, the MAH also aims to fulfil the Annex IID obligation from the approval of the neoadjuvant indication of Perjeta granted in 2015. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Annex II and the Package Leaflet have been updated accordingly.

The RMP version 10.0 has also been submitted." Request for 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004)

Action: For adoption

Request for Supplementary Information adopted on 14.12.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

The CHMP agreed to an additional 1-year of market protection.

5.1.9. Prolia - denosumab - EMEA/H/C/001120/II/0068

Amgen Europe B.V.

Rapporteur: Kristina Dunder, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Ulla Wändel Liminga

Scope: "Extension of Indication to include treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture for Prolia; as a consequence, sections 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. In addition, a minor change is made to the existing warning regarding sorbitol content in section 4.4 of the SmPC. The Package Leaflet is updated in accordance. The Risk Management Plan is also updated to version 24."

Action: For adoption

Request for Supplementary Information adopted on 09.11.2017, 22.06.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

5.1.10. Rapamune - sirolimus - EMEA/H/C/000273/II/0164

Pfizer Limited

Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga

Scope: "Extension of indication to include the treatment of patients with lymphangioliomyomatosis. As a consequence section 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) are updated in accordance. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling."

Action: For adoption

Request for Supplementary Information adopted on 25.01.2018, 20.07.2017.

The Committee discussed the issues identified in this application, mainly relating to the wording of the indication.

The Committee adopted a 3rd request for supplementary information with a specific timetable.

5.1.11. Tagrisso - osimertinib - EMEA/H/C/004124/II/0019

AstraZeneca AB

Rapporteur: Jorge Camarero Jiménez, Co-Rapporteur: Bjorg Bolstad, PRAC Rapporteur: Sabine Straus

Scope: "Extension of Indication to include (as monotherapy) first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, based on data from the FLAURA study (D5160C00007); a phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 versus a standard of care epidermal growth factor receptor-Tyrosine Kinase Inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic non-small-cell lung cancer.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, sections 4.4 and 4.8 of the SmPC have been updated with a new warning with regard to increased risk of developing adverse events of Grade 3 or higher in patients > 65 years and <50 kg. In addition, the MAH took the opportunity to update sections 2 and 4.4 of the SmPC with information regarding the excipient sodium, and to implement editorial changes in the SmPC and Package Leaflet.

An updated RMP version 10.0 was agreed during the procedure.

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies."

Action: For adoption

Request for Supplementary Information adopted on 22.02.2018.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

The CHMP agreed to an additional 1-year of market protection.

The CHMP noted the letter of recommendation dated 26 April 2018.

5.1.12. Translarna - ataluren - Orphan - EMEA/H/C/002720/II/0037

PTC Therapeutics International Limited

Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Sabine Straus

Scope: "Extension of Indication to include a new population (children from 2 to less than 5 years of age) for Translarna; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 7.1) is updated in accordance."

Action: For adoption

Request for Supplementary Information adopted on 22.02.2018, 14.12.2017.

The Committee discussed the issues identified in this application.

The Committee adopted a 3rd request for supplementary information with a specific timetable.

5.1.13. Venclyxto - venetoclax - Orphan - EMEA/H/C/004106/II/0008

AbbVie Limited

Rapporteur: Filip Josephson, PRAC Rapporteur: Patrick Batty

Scope: "Extension of Indication to include Venclyxto in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated.

The Package Leaflet is updated in accordance.

This submission also fulfils the Annex II condition to submit the results of the MURANO study comparing venetoclax plus rituximab to bendamustine plus rituximab in patients with relapsed/refractory CLL.

In addition, RMP version 3.0 is submitted."

Action: For adoption

The Committee discussed the issues identified in this application. The Committee discussed the available clinical data and whether the efficacy data was sufficient to support the extension of indication.

The Committee adopted a request for supplementary information with a specific timetable.

5.1.14. Xeljanz - tofacitinib - EMEA/H/C/004214/II/0006

Pfizer Limited

Rapporteur: Robert James Hemmings, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Sabine Straus

Scope: "Extension of Indication: Xeljanz in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease modifying antirheumatic drug (DMARD) therapy, supported by data from studies A3921091, A3921092, A3921125. 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 update the Annex II with minor editorial changes. The RMP version 3.2 has also been submitted."

Action: For adoption

Request for Supplementary Information adopted on 14.12.2017.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP

Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

5.1.15. [Xultophy - insulin degludec / liraglutide - EMEA/H/C/002647/II/0023](#)

Novo Nordisk A/S

Rapporteur: Kristina Dunder, PRAC Rapporteur: Menno van der Elst

Scope: "Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information based on cardiovascular outcomes studies conducted for each of the monocomponents of Xultophy: LEADER (Liraglutide Cardiovascular Outcomes Trial) and DEVOTE (Insulin Degludec Cardiovascular Outcomes Trial). Section 5.1 was also re-organised to improve reader friendliness.

The RMP version 7.0 has also been approved."

Action: For adoption

Request for Supplementary Information adopted on 22.02.2018.

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

5.1.16. [Yervoy - ipilimumab - EMEA/H/C/002213/II/0055](#)

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Sabine Straus

Scope: "Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 20.1) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the contact details of the Irish local representative in the Package Leaflet."

Action: For adoption

The Committee confirmed that all issues previously identified in this application had been addressed.

The Committee adopted a positive opinion by consensus together with the CHMP Assessment Report and translation timetable.

The Icelandic and Norwegian CHMP members were in agreement with the CHMP recommendations.

The summary of opinion was circulated for information.

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

5.2.1. **Darzalex - daratumumab - Orphan - EMEA/H/C/004077/II/0011**

Janssen-Cilag International NV

Rapporteur: Sinan B. Sarac, Co-Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: "Extension of Indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant for Darzalex; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 3.1 (in version 2 of the RMP template) has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the Package Leaflet."

Request by the applicant dated 24 April 2018 for an extension of clock stop to respond to the request for supplementary information adopted in March 2018

Action: For adoption

The CHMP agreed to the Request by the applicant for an extension of clock stop to respond to the request for supplementary information adopted in March 2018.

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

No items

6. **Ancillary medicinal substances in medical devices**

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

No items

6.2. **Update of Ancillary medicinal substances in medical devices**

6.2.1. **human fibrinogen / human thrombin - EMEA/H/D/004308**

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

Scope: Request by the applicant dated 10 April 2018 requesting an extension of clock stop to respond to the List of Questions adopted on 22 March 2018.

Action: For adoption

List of Questions adopted on 22.03.2018.

The CHMP agreed to the request by the applicant requesting an extension of clock stop to respond to the List of Questions adopted on 22 March 2018.

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

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

No items

8. Pre-submission issues

8.1. Pre-submission issue

No items

8.2. Priority Medicines (PRIME)

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

8.2.1. List of applications received

Action: For information

The CHMP noted the list of applications received.

8.2.2. Recommendation for PRIME eligibility

Action: For adoption

The CHMP adopted the recommendation for PRIME eligibility. The CHMP reviewed 3 recommendations for eligibility to PRIME: all 3 were denied. The individual outcomes are listed in PRIME Monthly Report on EMA website.

9. Post-authorisation issues

9.1. Post-authorisation issues

9.1.1. Flixabi - infliximab - EMEA/H/C/004020/MEA 007.1

Samsung Bioepis UK Limited (SBUK)

Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised PASS protocol in response to study nos.: SB2-G41-AS; SB2-G42-CD

Action: For adoption

The Committee discussed the PRAC advice.

The CHMP agreed by majority (22 out of 32 votes) recommending the deletion of the study from the RMP.

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

The recommendation will be sent to the PRAC.

9.1.2. Keytruda - pembrolizumab - EMEA/H/C/003820/ANX/018

Merck Sharp & Dohme Limited; treatment of urothelial cell cancer

Rapporteur: Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Sabine Straus

Scope: "Update on Study KEYNOTE-361 – Annex II condition (PAES) – protocol amendment"

Action: For adoption

The CHMP was updated on Study KEYNOTE-361.

9.1.3. Xagrid - anagrelide - EMEA/H/C/00480/S/0081

Shire Pharmaceutical Contracts Limited;

Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment procedure with proposal to switch from MA under exceptional circumstances to a standard MA.

Action: For adoption

The Committee adopted a positive opinion recommending the switching to a standard marketing authorisation by consensus together with the CHMP assessment report.

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

9.1.4. Zinbryta - daclizumab - EMEA/H/C/003862

Biogen Idec Ltd; treatment of multiple sclerosis (RMS)

Rapporteur: Bruno Sepodes, Co-Rapporteur: Greg Markey, PRAC Rapporteur: Eva A. Segovia

Scope: Letter from the applicant dated 1 March 2018 informing withdrawal of marketing authorisation

Action: For information

The CHMP noted the letter informing about the withdrawal of marketing authorisation.

9.1.5. Tecentriq – atezolizumab - EMEA/H/C/004143

Roche Registration GmbH; treatment of locally advanced or metastatic urothelial carcinoma (UC)

Rapporteur: Sinan B Sarac, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: "Update on Study IMvigor130 – Annex II condition (PAES) – protocol amendment"

Action: For adoption

The CHMP was updated on Study IMvigor130.

10. Referral procedures

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

No items

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

10.2.1. Gentamicin – EMEA/H/A-5(3)/1468

MAHs: various

Rapporteur: Nithyanandan Nagercoil, Co-Rapporteur: Jorge Camarero Jiménez

Scope: Start of procedure, appointment of Rapporteurs, list of questions, timetable

Action: For adoption

Review of histamine levels in Gentamicin-containing solutions for injection/infusion

The CHMP appointed Nithyanandan Nagercoil as Rapporteur and Jorge Camarero Jiménez as Co-Rapporteur.

The CHMP discussed the list of questions to the MAHs. The final list of questions together

with the timetable will be adopted via written procedure after the plenary meeting.

Post-meeting note: The final list of questions together with the timetable was adopted via written procedure on 30.04.2018.

Start of the procedure at CHMP: 30.04. 2018

List of questions to MAHs and List of questions to API manufacturers: 30.04.2018

Submission of responses: 14.06.2018

Re-start of the procedure: 28.06.2018

Rapporteur/co-rapporteur assessment reports circulated to CHMP: 11.07.2018

Comments: 16.07.2018

Updated Rapporteur/co-rapporteur assessment reports circulated to CHMP: 19.07.2018

CHMP list of outstanding issues /CHMP opinion: July 2018 CHMP

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

No items

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

10.4.1. Diclofenac Sodium Spray Gel 4% cutaneous spray, solution and associated names– EMEA/H/A-29(4)/1467

MAHs: various

Rapporteur: Nithyanandan Nagercoil, Co-Rapporteur: Harald Enzmann

Scope: Start of procedure, appointment of Rapporteurs, list of questions, timetable

Action: For adoption

Second wave of repeat use of MRP procedure

The CHMP appointed Nithyanandan Nagercoil as a Rapporteur and Harald Enzmann as a Co-Rapporteur.

The CHMP adopted a list of questions to the MAHs with a specific timetable.

Start of procedure (CHMP): April 2018 CHMP

List of Questions: 26.04.2018

Submission of responses: 17.05.2018

Re-start of the procedure: 31.05.2018

Rapporteurs assessment report(s) circulated to CHMP: 13.06.2018

Comments: 18.06.2018

Updated Rapporteur/co-rapporteur assessment reports circulated to CHMP: 21.06.018

LoOI/Opinion: June 2018 CHMP

10.4.2. Paclitaxel Hetero - EMEA/H/A-29(4)/1256

Hetero Europe S.L.

Rapporteur: Fátima Ventura, Co-Rapporteur: Paula Boudewina van Hennik

Scope: Start of procedure, appointment of Rapporteurs, list of questions, timetable

Action: For adoption

Decentralised Procedure number: PT/H/1256/001/DC, notification by the Portuguese Agency dated 29 March 2018 notifying of the start of a referral under Article 29(4) of Directive 2001/83/EC.

The CHMP appointed Fátima Ventura as a Rapporteur and Paula Boudewina van Hennik as a Co-Rapporteur.

The CHMP adopted a list of questions to the MAH with a specific timetable.

Start of procedure (CHMP): April 2018

List of Questions: 26.04.2018

Submission of responses: 14.06.2018

Re-start of the procedure: 28.06.2018

Rapporteur/co-rapporteur assessment report(s) circulated to CHMP: 11.07.2018

Comments: 16.07.2018

Updated Rapporteur/co-rapporteur assessment reports circulated to CHMP: 19 July 2018

CHMP LoOI or Opinion: July 2018 CHMP

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

No items

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

No items

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

No items

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

No items

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

No items

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

No items

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

No items

11. Pharmacovigilance issue

11.1. Early Notification System

April 2018 Early Notification System on envisaged CHMP/CMDh outcome accompanied by communication to the general public.

Action: For information

The CHMP noted the ENS.

12. Inspections

12.1. GMP inspections

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

12.2. GCP inspections

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

12.3. Pharmacovigilance inspections

Information related to Pharmacovigilance inspections will not be published as it undermines

the purpose of such inspections

12.4. GLP inspections

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

13. Innovation Task Force

13.1. Minutes of Innovation Task Force

No items

13.2. Innovation Task Force briefing meetings

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

13.2.1. ITF briefing meeting

Meeting date: 30 March 2018

Action: For adoption

The CHMP agreed to the ITF briefing meeting.

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

No items

13.4. Nanomedicines activities

No items

14. Organisational, regulatory and methodological matters

14.1. Mandate and organisation of the CHMP

14.1.1. Enhanced early dialogue to facilitate accelerated assessment of priority medicines (PRIME) – revision 1

Action: For adoption

The CHMP adopted the revised reflection paper.

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 9-12 April 2018

Action: For information

The CHMP noted the Summary of recommendations and advice.

List of Union Reference Dates and frequency of submission of Periodic Safety Update Reports (EURD list) for April 2018

Action: For adoption

The CHMP adopted the EURD list.

14.2.2. Committee for Advanced Therapies (CAT)

CAT draft minutes of meeting held on 18-20 April 2018

Action: For information

The CHMP noted the draft minutes.

14.2.3. Committee for Herbal Medicinal Products (HMPC)

Report from the HMPC meeting held on 26-27 March 2018

Action: For information

The CHMP noted the report.

14.2.4. Paediatric Committee (PDCO)

PIPs reaching D30 at April 2018 PDCO

Action: For information

The CHMP noted the information.

Report from the PDCO meeting held on 24 - 27 April 2018

Action: For information

The CHMP noted the report.

Joint CHMP/PDCO session

Agenda for joint session

Action: For discussion

Joint CHMP/PDCO session was held.

14.2.5. Committee for Orphan Medicinal Products (COMP)

Report from the COMP meeting held on 17-19 April 2018

Action: For information

The CHMP noted the report.

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

Report from the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on the meeting held on 23-25 April 2018

Action: For information

The CHMP noted the report.

CMDh questions to PGWP on flecainide (PSUSA/00001396/201706)

Action: For adoption

The CHMP agreed to the questions to PGWP.

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 9-12 April 2018. 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.

The CHMP noted the report.

14.3.2. Biologics Working Party (BWP)

Chair: Sol Ruiz/Nanna Aaby Kruse

Reports from BWP April 2018 meeting to CHMP for adoption:

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

Action: For adoption

The CHMP adopted the BWP reports.

14.3.3. Biostatistics Working Party (BSWP)

Chair: Anja Schiel/Jörg Zinserling

Nomination of additional assessor to BSWP

Action: For adoption

The CHMP agreed to Wolfgang Jacquet (BE) as additional assessor to BSWP.

14.3.4. Blood Products Working Party (BPWP)

Chair: Jacqueline Kerr

Nomination of new alternate member to BPWP

Action: For adoption

The CHMP agreed to Claire-Li Ding (FR) as alternate member to BPWP.

Nomination of additional assessor to the BPWP

Action: For adoption

Postponed

14.3.5. Cardiovascular Working Party (CVSWP)

Chair: Kristina Dunder

Election of a new vice-chair of Cardiovascular Working Party (CVSWP), the mandate of the previous vice-chair ended in December 2017 when Kristina Dunder was elected as Chair.

Action: For adoption

The CHMP elected Alar Irs as Vice-Chair to CVSWP.

Nomination of additional assessor to the CVSWP

Action: For adoption

The CHMP agreed to Denisse Mazilu (RO) as additional assessor to CVSWP.

14.3.6. Rheumatology/Immunology Working Party (RIWP)

Chair: Jan Mueller-Berghaus

Nomination of additional assessor to the RIWP

Action: For adoption

The CHMP agreed to Carolina Negrei (RO) as additional assessor to RIWP.

14.3.7. Safety Working Party (SWP)

Chair: Jan Willem Van der Laan

Nomination of new alternate member to SWP

Action: For adoption

The CHMP agreed to Nikolina Torti (HR) as new alternate member to SWP.

14.3.8. Modelling and Simulation Working Group (MSWG)

Chair (acting): Flora Musuamba Tshinanu

Conversion of MSWG to MSWP

In view of the current and anticipated impact of M&S approaches in drug development and regulatory review it is proposed to convert the EMA MSWG to a CHMP temporary working party

Action: For adoption

The CHMP agreed to the conversion of the Modelling and Simulation Working Group to a working party. The CHMP will be updated on the details of member nomination and chair election at the next meeting.

Post meeting note: Call for nomination of members and experts including their CV to be sent by 25 May 2018.

Call for interest for Chair/Vice-Chair

Action: For adoption

Postponed

14.3.9. Ad-hoc Influenza Working Group

Chair: Ton van der Stappen

Scope: Amended EU Strain selection for the Influenza Vaccines for the Season 2018/2019: Report from the Ad Hoc Influenza working group to the BWP (EMA/CHMP/BWP/209017/2018)

Action: For adoption

The CHMP adopted the amended report.

Scope: Amended EU Recommendation for the Seasonal Influenza Vaccine Composition for the Season 2018/2019 (EMA/CHMP/BWP/209019/2018)

Action: For adoption

The CHMP adopted the amended EU recommendation.

14.3.10. Pharmacogenomics Working Party (PGWP)

Chair: Krishna Prasad/Markus Paulmichl

Nomination of additional assessor to the PGWP

Action: For adoption

The CHMP agreed to Nikica Mirošević Skvrce (HR) as additional assessor to PGWP.

14.3.11. Temporary working parties and drafting groups composition

Action: For information

The CHMP noted the temporary working parties and drafting groups' composition.

14.3.12. The Active Substance Master File Working Group (ASMF WG)

ASMF Worksharing Procedure User Guide (EMA/CMDh/251114/2018)

Action: For adoption

The CHMP adopted the ASMF user guide.

14.4. Cooperation within the EU regulatory network

No items

14.5. Cooperation with International Regulators

14.5.1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – EMA/CHMP representation

Action: For information

The CHMP agreed that Tomas Salmonson should represent EMA/CHMP at the ICH meeting in November 2018.

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

No items

14.7. CHMP work plan

No items

14.8. Planning and reporting

No items

14.9. Others

No items

15. Any other business

15.1. AOB topic

15.1.1. Preparedness of the system and capacity increase

Action: For information

The CHMP noted the update.

15.1.2. Update on EMA relocation

Action: For information

The CHMP noted the update. There is a tracking tool on the relocation published on EMA website:

http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500244941

The temporary building, the Spark building is available as of 1 January 2019. The EMA is scheduled to be fully operational in temporary premises as of 30 March 2019.

15.1.3. Article 58: Update from the March 2017 'Malta' CHMP meeting with African regulators

Action: For information

Postponed to May CHMP

15.1.4. Information on the legislative proposal for HTA collaboration

Action: For information

The CHMP noted the update.

16. List of participants

List of participants including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 23 – 26 April 2018 meeting

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tomas Salmonson	Chair	Sweden	No interests declared	
Andrea Laslop	Member	Austria	No interests declared	
Milena Stain	Alternate	Austria	No interests declared	
Bart Van der Schueren	Member	Belgium	No interests declared	
Christophe Focke	Alternate	Belgium	No restrictions applicable to this meeting	
Mila Vlaskovska	Member	Bulgaria	No interests declared	
Katarina Vučić	Member	Croatia	No interests declared	
Emilia Mavrokordatou	Member	Cyprus	No interests declared	
Ondřej Slanař	Member	Czech Republic	No interests declared	
Sinan B. Sarac	Member	Denmark	No interests declared	
Mark Ainsworth	Alternate	Denmark	No participation in final deliberations and voting on:	5.1.15. Xultophy - insulin degludec / liraglutide - EMEA/H/C/002647/II/0023
Alar Irs	Member	Estonia	No restrictions applicable to this meeting	
Outi Mäki-Ikola	Member	Finland	No restrictions applicable to this meeting	
Tuomo Lapveteläinen	Alternate	Finland	No interests declared	
Alexandre Moreau	Member	France	No interests declared	
Joseph Emmerich	Alternate	France	No interests declared	
Harald Enzmann	Member (Vice-Chair)	Germany	No interests declared	
Martina Weise	Alternate	Germany	No restrictions applicable to this meeting	
Maria Orfanou	Alternate	Greece	No interests declared	
Agnes Gyurasics	Member	Hungary	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kolbeinn Gudmundsson	Member	Iceland	No interests declared	
Jayne Crowe	Member	Ireland	No interests declared	
Daniela Melchiorri	Member	Italy	No restrictions applicable to this meeting	
Natalja Karpova	Alternate	Latvia	No interests declared	
Romaldas Mačiulaitis	Member	Lithuania	No participation in final deliberations and voting on:	5.1.8. Perjeta - pertuzumab - EMEA/H/C/002547/II/0034 9.1.6. Tecentriq – atezolizumab - EMEA/H/C/004143
Jacqueline Genoux-Hames	Member	Luxembourg	No interests declared	
Carola de Beaufort	Alternate	Luxembourg	No interests declared	
John Joseph Borg	Member	Malta	No interests declared	
Helen Vella	Alternate	Malta	No interests declared	
Johann Lodewijk Hillege	Member	Netherlands	No interests declared	
Paula Boudewina van Hennik	Alternate	Netherlands	No interests declared	
Svein Rune Andersen	Member	Norway	No interests declared	
Bjorg Bolstad	Alternate	Norway	No restrictions applicable to this meeting	
Ewa Balkowiec Iskra	Member	Poland	No interests declared	
Bruno Sepodes	Member	Portugal	No interests declared	
Fatima Ventura	Alternate	Portugal	No restrictions applicable to this meeting	
Simona Badoi	Member	Romania	No interests declared	
Francisek Drafi	Member	Slovakia	No interests declared	
Rajko Kenda	Member	Slovenia	No restrictions applicable to this meeting	
Concepcion Prieto Yerro	Member	Spain	No interests declared	
Jorge Camarero Jiménez	Alternate	Spain	No participation in final deliberations and voting on:	5.1.8. Perjeta - pertuzumab - EMEA/H/C/002547/II/0034 9.1.6. Tecentriq – atezolizumab - EMEA/H/C/004143
Kristina Dunder	Member	Sweden	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Filip Josephson	Alternate	Sweden	No interests declared	
Greg Markey	Member	United Kingdom	No interests declared	
Nithyanandan Nagercoil	Alternate	United Kingdom	No restrictions applicable to this meeting	
Robert James Hemmings	Co-opted member	United Kingdom	No restrictions applicable to this meeting	
Koenraad Norga	Co-opted member	Belgium	No participation in final deliberations and voting on:	3.3.2. zanamivir - EMEA/H/C/004102
Jan Mueller-Berghaus	Co-opted member	Germany	No interests declared	
Blanka Hirschlerova	Co-opted member	Czech Republic	No interests declared	
Sol Ruiz	Co-opted member	Spain	No interests declared	
Patricia Diaz Ramos	Expert - in person*	Spain	No interests declared	
Sabine Mayrhofer	Expert - in person*	Germany	No interests declared	
Kristina Bech Jensen	Expert - in person*	Denmark	No interests declared	
Sylvain Gueho	Expert - in person*	France	No interests declared	
Kirsi Åkerberg	Expert - in person*	Finland	No interests declared	
Peter Morgan Warren	Expert - in person*	United Kingdom	No interests declared	
Martina Schussler-Lenz	Expert - via telephone*	Germany	No interests declared	
Koenraad Brusselmans	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	
Olga Kholmanskikh	Expert - via telephone*	Belgium	No interests declared	
Mair Powell	Expert - via telephone*	United Kingdom	No interests declared	
Marta Soler Soneira	Expert - via telephone*	Spain	No interests declared	
Martijn van Gils	Expert - via telephone*	Netherlands	No interests declared	
Inkie Evers van Gogh	Expert - via telephone*	Netherlands	No restrictions applicable to this meeting	
Didier Meulendijks	Expert - via telephone*	Netherlands	No restrictions applicable to this meeting	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ulla Wändel Liminga	Expert - via telephone*	Sweden	No interests declared	
Maria Luttgen	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	
Macarena Rodriguez Mendizabal	Expert - via telephone*	Spain	No interests declared	
Regine Magdalene Lehnert	Expert - via telephone*	Germany	No interests declared	
Nele Berthels	Expert - via Adobe*	Belgium	No interests declared	
George Aislaitner	Expert - via Adobe*	Germany	No interests declared	
Christine Greiner	Expert – via Adobe*	Germany	No interests declared	
Patients' representative	Patient observer		No interests declared	
Patients' representative	Patient observer		No interests declared	
Representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

*Experts were only evaluated against the product(s) they have been invited to talk about.

17. Explanatory notes

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

Oral explanations (section 2)

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

Initial applications (section 3)

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

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

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



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

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

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

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

Extensions of marketing authorisations are applications for the change or addition of new strengths,

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

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

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

Ancillary medicinal substances in medical devices *(section 6)*

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

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

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

Re-examination procedures *(section 5.3)*

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

Withdrawal of application *(section 3.7)*

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

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

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

Pre-submission issues *(section 8)*

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

Post-authorisation issues *(section 9)*

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

Referral procedures *(section 10)*

This section lists referrals that are ongoing or due to be started at the plenary meeting. A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a

particular medicine or class of medicines on behalf of the EU. Further information on such procedures can be found [here](#).

Pharmacovigilance issues (section 11)

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

Inspections Issues (section 12)

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

Innovation task force (section 13)

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

Scientific advice working party (SAWP) (section 14.3.1)

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

Satellite groups / other committees (section 14.2)

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

Invented name issues (section 14.3)

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

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



14 June 2018
EMA/CHMP/406365/2018

Annex to 23-26 April 2018 CHMP Minutes

Pre submission and post authorisations issues

A. PRE SUBMISSION ISSUES	4
A.1. ELIGIBILITY REQUESTS.....	4
A.2. Appointment of Rapporteur / Co-Rapporteur Full Applications	4
A.3. PRE-SUBMISSION ISSUES FOR INFORMATION	4
B. POST-AUTHORISATION PROCEDURES OUTCOMES	4
B.1. Annual re-assessment outcomes	4
B.1.1. Annual reassessment for products authorised under exceptional circumstances	4
B.2. RENEWALS OF MARKETING AUTHORISATIONS OUTCOMES.....	4
B.2.1. Renewals of Marketing Authorisations requiring 2nd Renewal	4
B.2.2. Renewals of Marketing Authorisations for unlimited validity.....	5
B.2.3. Renewals of Conditional Marketing Authorisations.....	6
B.3. POST-AUTHORISATION PHARMACOVIGILANCE OUTCOMES.....	7
B.4. EPARs / WPARs	13
B.5. TYPE II VARIATION, WORKSHARING PROCEDURE OUTCOMES	15
B.5.1. CHMP assessed procedures scope: Pharmaceutical aspects	15
B.5.2. CHMP assessed procedures scope: Non-Clinical and Clinical aspects	18
B.5.3. CHMP-PRAC assessed procedures	31
B.5.4. PRAC assessed procedures.....	40
B.5.5. CHMP-CAT assessed procedures	49
B.5.6. CHMP-PRAC-CAT assessed procedures	50
B.5.7. PRAC assessed ATMP procedures	50
B.5.8. Unclassified procedures and worksharing procedures of type I variations.....	50
B.5.9. Information on withdrawn type II variation / WS procedure	53
B.5.10. Information on type II variation / WS procedure with revised timetable.....	53
B.6. START OF THE PROCEDURES TIMETABLES FOR INFORMATION	54
B.6.1. Start of procedure for New Applications: timetables for information	54
B.6.2. Start of procedure for Extension application according to Annex I of Reg. 1234/2008): timetables for information	55
B.6.3. Restart of procedure - responses received to Day 120 List of Questions timetables: for information.....	56



B.6.4. Annual Re-assessments: timetables for adoption	58
B.6.5. Renewals of Marketing Authorisations: timetables for adoption provided only if the validation has been completed	59
B.6.6. VARIATIONS – START OF THE PROCEDURE.....	59
B.6.7. Type II Variations scope of the Variations: Extension of indication	59
B.6.8. CHMP assessed procedures scope: Pharmaceutical aspects	63
B.6.9. CHMP assessed procedures scope: Non-Clinical and Clinical aspects	65
B.6.10. CHMP-PRAC assessed procedures.....	72
B.6.11. PRAC assessed procedures.....	76
B.6.12. CHMP-CAT assessed procedures	77
B.6.13. CHMP-PRAC-CAT assessed procedures.....	77
B.6.14. PRAC assessed ATMP procedures	77
B.6.15. Unclassified procedures and worksharing procedures of type I variations	77
B.7. DOCUMENTS TABLED IN MMD AFTER THE CHMP PLENARY.....	79
B.7.1. Yearly Line listing for Type I and II variations.....	79
B.7.2. Monthly Line listing for Type I variations.....	79
B.7.3. Opinion on Marketing Authorisation transfer (MMD only)	79
B.7.4. Notifications in accordance with Article 61(3) of Council Directive 2001/83/EC (MMD only)	79
B.7.5. Request for supplementary information relating to Notification of Type I variation (MMD only)	79
B.7.6. Notifications of Type I Variations (MMD only)	79
C. Annex C - Post-Authorisation Measures (PAMs), (Line listing of Post authorisation measures with a description of the PAM. Procedures starting in that given month with assessment timetabled)	79
D. Annex D - Post-Authorisation Measures (PAMs), (Details on PAMs including description and conclusion, for adoption by CHMP in that given month, or finalised ones with PRAC recommendation and no adoption by CHMP needed)	79
E. Annex E - EMEA CERTIFICATION OF PLASMA MASTER FILES	79
E.1. PMF Certification Dossiers:.....	79
E.1.1. Annual Update.....	79
E.1.2. Variations:	79
E.1.3. Initial PMF Certification:.....	79
E.2. Time Tables – starting & ongoing procedures: For information	79
F. ANNEX F - Decision of the Granting of a Fee Reduction/Fee Waiver	80
F.1. Parallel Distribution - Pursuant to Article 9 of Council Regulation (EC) No. 2743/98 of 14 December 1998, as amended.....	80
F.2. Request for scientific opinion on justification of exceptional circumstance and for imperative grounds of public health.....	80
G. ANNEX G.....	80
G.1. Final Scientific Advice (Reports and Scientific Advice letters):	80
G.2. Ongoing procedures	80
G.3. PRIME.....	80
G.3.1. List of procedures concluding at 23-26 April 2018 CHMP plenary:	80
G.3.2. List of procedures starting in April 2018 for May 2018 CHMP adoption of outcomes..	80

H. ANNEX H - Product Shared Mailboxes – e-mail address80

A. PRE SUBMISSION ISSUES

A.1. ELIGIBILITY REQUESTS

Report on Eligibility to Centralised Procedure for April 2018: **For adoption** Adopted

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

Final Outcome of Rapporteurship allocation for April 2018: **For adoption** Adopted

A.3. PRE-SUBMISSION ISSUES FOR INFORMATION

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

B. POST-AUTHORISATION PROCEDURES OUTCOMES

B.1. Annual re-assessment outcomes

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

SCENESSE - afamelanotide - EMA/H/C/002548/S/0019, Orphan Clinuvel (UK) Limited, Rapporteur: Harald Enzmann, PRAC Rapporteur: Valerie Strassmann	Positive Opinion adopted by consensus together with the CHMP assessment report. The Marketing Authorisation remains under exceptional circumstances. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP opinion.
Xagrid - anagrelide - EMA/H/C/000480/S/0081 Shire Pharmaceutical Contracts Limited, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni	See 9.1

B.2. RENEWALS OF MARKETING AUTHORISATIONS OUTCOMES

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

Defitelio - defibrotide - EMA/H/C/002393/R/0032, Orphan Gentium S.r.l., Rapporteur: Nithyanandan Nagercoil, Co-Rapporteur: Kristina Dunder, PRAC Rapporteur: Julie Williams	Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable. Based on the review of the available information, the CHMP was of the opinion that an additional five-year renewal was required.
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	The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.
<p>Imnovid - pomalidomide - EMEA/H/C/002682/R/0028, Orphan Celgene Europe Limited, Rapporteur: Robert James Hemmings, Co-Rapporteur: Jorge Camarero Jiménez, PRAC Rapporteur: Patrick Batty Request for Supplementary Information adopted on 22.02.2018.</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that an additional five-year renewal was required.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>Xofigo - radium-223 - EMEA/H/C/002653/R/0030 Bayer AG, Rapporteur: Harald Enzmann, Co-Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Patrick Batty</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that an additional five-year renewal was required.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>B.2.2. Renewals of Marketing Authorisations for unlimited validity</p>	
<p>Corbilta - levodopa / carbidopa / entacapone - EMEA/H/C/002785/R/0015 Orion Corporation, Rapporteur: Outi Mäki-Ikola, Co-Rapporteur: Bruno Sepodes, PRAC Rapporteur: Kirsti Villikka</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that the renewal of the marketing authorisation can be granted with unlimited validity.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>Evicel - human fibrinogen / human thrombin - EMEA/H/C/000898/R/0054 Omrix Biopharmaceuticals N. V., Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Ewa Balkowiec Iskra, PRAC Rapporteur: Brigitte Keller-Stanislawski Request for Supplementary Information adopted on 26.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>Inflectra - infliximab - EMEA/H/C/002778/R/0056 Hospira UK Limited, Duplicate, Duplicate of Remsima, Rapporteur: Greg Markey, Co-Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Patrick Batty Request for Supplementary Information adopted</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that the renewal of the marketing authorisation can</p>

<p>on 22.02.2018.</p>	<p>be granted with unlimited validity.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>Lemtrada - alemtuzumab - EMEA/H/C/003718/R/0020 Genzyme Therapeutics Ltd, Duplicate, Duplicate of Lemtrada (WD), Rapporteur: Mark Ainsworth, Co-Rapporteur: Filip Josephson, PRAC Rapporteur: Anette Kirstine Stark Request for Supplementary Information adopted on 22.03.2018.</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that the renewal of the marketing authorisation can be granted with unlimited validity.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>Nexium Control - esomeprazole - EMEA/H/C/002618/R/0021 Pfizer Consumer Healthcare Limited, Rapporteur: Romaldas Mačiulaitis, Co-Rapporteur: Robert James Hemmings, PRAC Rapporteur: Simona Kudeliene Request for Supplementary Information adopted on 22.02.2018.</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that the renewal of the marketing authorisation can be granted with unlimited validity.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>
<p>Remsima - infliximab - EMEA/H/C/002576/R/0047 Celltrion Healthcare Hungary Kft., Rapporteur: Greg Markey, Co-Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Patrick Batty Request for Supplementary Information adopted on 22.02.2018.</p>	<p>Positive Opinion adopted by consensus together with the CHMP assessment report and translation timetable.</p> <p>Based on the review of the available information, the CHMP was of the opinion that the renewal of the marketing authorisation can be granted with unlimited validity.</p> <p>The Icelandic and Norwegian CHMP Members were in agreement with the CHMP Opinion.</p>

B.2.3. Renewals of Conditional Marketing Authorisations

<p>Translarna - ataluren - EMEA/H/C/002720/R/0041, Orphan PTC Therapeutics International Limited, Rapporteur: Johann Lodewijk Hillege, Co-Rapporteur: Concepcion Prieto Yerro, PRAC Rapporteur: Sabine Straus Request for Supplementary Information adopted on 26.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>Zalmoxis - allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor</p>	<p>Request for supplementary information adopted with a specific timetable.</p>

(ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - EMEA/H/C/002801/R/0010, Orphan, ATMP

MolMed SpA, Rapporteur: Johannes Hendrikus Ovelgonne, CHMP Coordinator: Paula Boudewina van Hennik, PRAC Rapporteur: Brigitte Keller-Stanislawski

Request for Supplementary Information adopted on 20.04.2018.

B.3. POST-AUTHORISATION PHARMACOVIGILANCE OUTCOMES

Signal detection

Noted.

PRAC recommendations on signals adopted at the PRAC meeting held on 9-12 April 2018
PRAC:

Signal of CMV reactivation

Adopted.

Aprycel - Dasatinib - EMEA/H/C/000709

Bristol-Myers Squibb Pharma EEIG,
Rapporteur: Sinan B. Sarac, Co-Rapporteur: Fátima Ventura

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

Signal of pulmonary hypertension

Adopted.

Tyverb – Lapatinib - EMEA/H/C/000795

Novartis Europharm Limited, Rapporteur: Filip Josephson, Co-Rapporteur: Bruno Sepodes
PRAC recommendation on a variation: **For adoption**

Signal of angioedema and urticaria

Adopted.

Brintellix – Vortioxetine -

EMEA/H/C/002717

H. Lundbeck A/S, Rapporteur: Bart Van der Schueren, Co-Rapporteur: Martina Weise

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

PSUR procedures for which PRAC adopted a recommendation for variation of the terms of the MA at its April 2018 meeting:

EMEA/H/C/PSUSA/00000931/201709

(daptomycin)

CAPS:

Cubicin (EMEA/H/C/000637) (daptomycin), Merck Sharp & Dohme Limited, Rapporteur: Greg Markey, PRAC Rapporteur: Julie Williams, "12 Sep 2016 to 11 Sep 2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned

	<p>medicinal product(s), concerning the following change(s):</p> <p>Update of section 4.8 of the SmPC to add thrombocytopenia as new adverse reaction with an unknown frequency. The Package leaflet is updated accordingly.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.</p>
<p>EMA/H/C/PSUSA/00001205/201709 (eltrombopag) CAPS: Revolade (EMA/H/C/001110) (eltrombopag / eltrombopag olamine), Novartis Europharm Limited, Rapporteur: Concepcion Prieto Yerro, PRAC Rapporteur: Eva A. Segovia, "01-Oct-2016 to 30-Sep-2017."</p>	<p>The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):</p> <p>Update of section 4.4 of the SmPC to add a warning on potential laboratory test interferences.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.</p>
<p>EMA/H/C/PSUSA/00002285/201708 (pantoprazole) CAPS: CONTROLOC Control (EMA/H/C/001097) (pantoprazole), Takeda GmbH, Rapporteur: Greg Markey PANTOLOC Control (EMA/H/C/001100) (pantoprazole), Takeda GmbH, Rapporteur: Greg Markey PANTOZOL Control (EMA/H/C/001013) (pantoprazole), Takeda GmbH, Rapporteur: Greg Markey SOMAC Control (EMA/H/C/001098) (pantoprazole), Takeda GmbH, Rapporteur: Greg Markey NAPS: ANAGASTRA - TAKEDA GMBH (KONSTANZ) APTON - LABORATÓRIOS DELTA, S.A. CONTROLOC - TAKEDA PHARMA SP.Z.O.O CONTROLOC - MUNDIPHARMA PHARMACEUTICALS LTD CONTROLOC - TAKEDA PHARMACEUTICALS CROATIA D.O.O. CONTROLOC I.V. - TAKEDA HELLAS S.A.</p>	<p>The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):</p> <p>Update of section 4.8 of the SmPC to add the adverse reaction paraesthesia and hypocalcaemia with a frequency of "not known". The Package leaflet is updated accordingly.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.</p>

EUPANTOL - TAKEDA FRANCE S.A.S.
INIPOMP - TAKEDA FRANCE S.A.S.
KAIROL - FARMOZ - SOCIEDADE TÉCNICO
MEDICINAL, S.A
PANTECTA - TAKEDA ITALIA S.P.A.
PANTECTA - TAKEDA GMBH (KONSTANZ)
PANTOC - TAKEDA FARMACEUTICOS
PORTUGAL LDA.
PANTOC I.V. - TAKEDA FARMACEUTICOS
PORTUGAL LDA.
PANTOLOC - TAKEDA PHARMA GES.M.B.H
PANTOLOC - TAKEDA PHARMA A/S
PANTOPAN - TAKEDA ITALIA S.P.A.
PANTOPRAZOL ALTAN - TAKEDA
FARMACEUTICOS PORTUGAL LDA.
PANTOPRAZOL BYK - TAKEDA GMBH
(KONSTANZ)
PANTOPRAZOL NYC - TAKEDA GMBH
(KONSTANZ)
PANTOPRAZOL NYCOMED - TAKEDA GMBH
(KONSTANZ)
PANTOPRAZOL SANDOZ - SANDOZ
PHARMACEUTICALS D.D.
PANTOPRAZOL TEVA - TEVA
PHARMACEUTICALS POLSKA SP. Z O.O.
PANTOPRAZOLE BRISTOL LABORATORIES -
BRISTOL LABORATORIES LTD (BERKHAMSTED)
PANTOPRAZOLE TAKEDA UK - TAKEDA UK
LTD
PANTORC - TAKEDA ITALIA S.P.A.
PANTOZOL - TAKEDA NEDERLAND BV
PANTOZOL - TAKEDA BELGIUM SCA/CVA
PANTOZOL I.V. - TAKEDA NEDERLAND BV,
TAKEDA GMBH (KONSTANZ)
PEPTAZOL - RECORDATI INDUSTRIA CHIMICA
E FARMACEUTICA S.P.A
PEPTAZOL - RECORDATI INDUSTRIA CHIMICA
E FARMACEUTICA S.P.A.
PRAZOLACID - PHARMASWISS ČESKÁ
REPUBLIKA S.R.O.
PROTIUM - TAKEDA UK LTD
PROTIUM I.V. - TAKEDA UK LTD
RIFUN - TAKEDA GMBH (KONSTANZ)
SOMAC - TAKEDA AS, TAKEDA GMBH
(KONSTANZ)
TECTA - TAKEDA GMBH (KONSTANZ)
ULCOTENAL - TAKEDA GMBH (KONSTANZ)
ZURCAL - TAKEDA GMBH (KONSTANZ)
ZURCAL - TAKEDA FARMACEUTICOS
PORTUGAL LDA. TAKEDA AUSTRIA GMBH
ZURCAZOL - TAKEDA HELLAS S.A.

ZURCAZOL I.V. - TAKEDA HELLAS S.A.
КОНТРОЛОК - TAKEDA GMBH (KONSTANZ)
PRAC Rapporteur: Patrick Batty,
"24 August 2012 to 23 August 2017"

EMA/H/C/PSUSA/00002653/201709
(rivaroxaban)
CAPS:
Xarelto (EMA/H/C/000944) (rivaroxaban),
Bayer AG, Rapporteur: Kristina Dunder, PRAC
Rapporteur: Qun-Ying Yue, "16-Sep-2016 to 15-
Sep-2017"

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing rivaroxaban remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows: Update of section 4.4, 4.5 and 4.8 of the SmPC. The Package leaflet is updated accordingly.

The MAH should address the following issues in the next PSUR:

- Provide a summary tabulation of all ADRs and a tabulation of reported ADRs according to SOC.
- To present in a cumulative tabulation all cases where diagnosis of vasculitis has been confirmed by biopsy (or other reliable method of diagnosis), including a temporal relationship and information on dechallenge/ rechallenge, medical history and concomitant medications. A detailed discussion and analysis of the cases should also be provided.

In future PSURs, the MAH should continuously present new cases of hepatic failure. The MAH is also requested to present new cases of medically confirmed esophagitis in upcoming PSURs.

For future cumulative reviews, the MAH is requested to provide also the complete case narratives (CIOMS reports) of all cases included in the review, e.g. enclosed as a line listing in an Appendix to the PSUR.

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

The MAH should be reminded that the PSUR procedure is not appropriate for submission of CSRs. The PSUR is not the appropriate procedure for submitting final or interim study reports to the EU regulatory authorities. Final study reports should be submitted and assessed via the appropriate procedure in line with the

EMA/H/C/PSUSA/00003001/201709

(trabectedin)

CAPS:

Yondelis (EMA/H/C/000773) (trabectedin),
Pharma Mar, S.A., Rapporteur: Sinan B. Sarac,
PRAC Rapporteur: Doris Stenver, "18
September 2016 to 17 September 2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus, the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):

Update of section 4.4 and 4.8 of the SmPC to add additional information to the warning on Capillary Leak Syndrome. The Package leaflet is updated accordingly.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

EMA/H/C/PSUSA/00009119/201709

(denosumab (indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone))

CAPS:

XGEVA (EMA/H/C/002173) (denosumab),
Amgen Europe B.V., Rapporteur: Kristina
Dunder, PRAC Rapporteur: Ulla Wändel Liminga,
"27 September 2016 - 26 September 2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus, the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):

Update of section 4.8 of the SmPC to add information regarding the risk of 'new primary malignancy' in the course of XGEVA treatment including the numbers of relevant cases reported in clinical trials and the cumulative incidence overtime. The Package leaflet is updated accordingly.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

EMA/H/C/PSUSA/00010133/201709

(regorafenib)

CAPS:

Stivarga (EMA/H/C/002573) (regorafenib),
Bayer AG, Rapporteur: Paula Boudewina van
Hennik, PRAC Rapporteur: Sabine Straus, "27-
Sep-2016 to 26-Sep-2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):

Update of the SmPC section 4.8 to include 'peripheral neuropathy' with the frequency common. The Package leaflet is updated

accordingly.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

EMA/H/C/PSUSA/00010311/201709

(dulaglutide)

CAPS:

Trulicity (EMA/H/C/002825) (dulaglutide), Eli Lilly Nederland B.V., Rapporteur: Greg Markey, PRAC Rapporteur: Carmela Macchiarulo, "19-March-2017 – 18-September-2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):

Update of section 4.8 of the SmPC to add the adverse reactions Cholelithiasis and Cholecystitis with a frequency uncommon. The Package leaflet is updated accordingly.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

EMA/H/C/PSUSA/00010366/201709

(naltrexone / bupropion)

CAPS:

Mysimba (EMA/H/C/003687) (naltrexone hydrochloride / bupropion hydrochloride), Orexigen Therapeutics Ireland Limited, Rapporteur: Mark Ainsworth, PRAC Rapporteur: Martin Huber, "10 March to 9 September 2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation for the above mentioned medicinal product(s), concerning the following change:

Update of section 4.8 of the SmPC to add "urticaria" as an adverse reactions of the naltrexone/bupropion fixed-combination with the frequency "uncommon".

EMA/H/C/PSUSA/00010368/201709

(oritavancin)

CAPS:

Orbactiv (EMA/H/C/003785) (oritavancin), The Medicines Company UK Limited, Rapporteur: Greg Markey, PRAC Rapporteur: Adam Przybylkowski, "from 20 March 2017 to 19 September 2017"

The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus, the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):

Update of section 4.4 of the SmPC to add to add a warning on Red Man Syndrome and section 4.8 to add Red Men Syndrome as new adverse reaction with a rare frequency. The Package leaflet is updated accordingly.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned

<p>EMA/H/C/PSUSA/00010403/201709 (pembrolizumab) CAPS: Keytruda (EMA/H/C/003820) (pembrolizumab), Merck Sharp & Dohme Limited, Rapporteur: Daniela Melchiorri, PRAC Rapporteur: Sabine Straus, "04/03/2017-03/09/2017"</p>	<p>recommendation of the CHMP.</p> <p>The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):</p> <p>Update of section 4.8 of the SmPC to add pericarditis and pericardial effusion as new adverse drug reactions (ADR) with a frequency uncommon and to add a footnote to the existing ADR 'myasthenic syndrome' to indicate that the event 'myasthenia gravis' is included. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes and corrections in the SmPC.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.</p>
<p>EMA/H/C/PSUSA/00010499/201709 (eftrenonacog alfa) CAPS: Alprolix (EMA/H/C/004142) (eftrenonacog alfa), Swedish Orphan Biovitrum AB (publ), Rapporteur: Andrea Laslop, PRAC Rapporteur: Brigitte Keller-Stanislawski, "20 March 2017 to 19 September 2017"</p>	<p>The CHMP, having considered in accordance with Article 28 of Regulation (EC) No 726/2004 the PSUR on the basis of the PRAC recommendation and the PRAC assessment report as appended, recommends by consensus the variation to the terms of the marketing authorisation(s) for the above mentioned medicinal product(s), concerning the following change(s):</p> <p>Update of sections 4.4 and 4.8 of the SmPC to update the information on hypersensitivity and anaphylaxis.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.</p>
<p>B.4. EPARs / WPARs</p>	
<p>Aplidin - plitidepsin - EMA/H/C/004354, Orphan Pharma Mar, S.A., treatment of multiple myeloma, New active substance (Article 8(3) of Directive No 2001/83/EC)</p>	<p>For information only. Comments can be sent to the EPL in case necessary.</p>
<p>Juluca - dolutegravir / rilpivirine - EMA/H/C/004427</p>	<p>For information only. Comments can be sent to the EPL in case necessary.</p>

ViiV Healthcare UK Limited, treatment of HIV,
Fixed combination application (Article 10b of
Directive No 2001/83/EC)

**KANJINTI - trastuzumab -
EMA/H/C/004361**

Amgen Europe B.V., BREDA, treatment of
metastatic breast cancer, early breast cancer,
metastatic gastric cancer, Similar biological
application (Article 10(4) of Directive No
2001/83/EC)

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

**Pemetrexed Krka - pemetrexed -
EMA/H/C/003958**

KRKA d.d., Novo mesto, treatment of malignant
pleural mesothelioma and non-small cell lung
cancer, Generic, Generic of Alimta, Generic
application (Article 10(1) of Directive No
2001/83/EC)

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

**Prasugrel Mylan - prasugrel -
EMA/H/C/004644**

Mylan S.A.S, prevention of atherothrombotic
events, Generic, Generic of Efient, Generic
application (Article 10(1) of Directive No
2001/83/EC)

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

**PROHIPUR - sodium benzoate -
EMA/H/C/004150, Orphan**

Lucane Pharma, treatment of non ketotic
hyperglycinemia, urea cycle disorders including
carbamoyl-phosphate synthase-1 deficiency,
ornithine transcarbamylase deficiency,
citrullinaemia type 1, argininosuccinic aciduria,
hyperargininaemia, n-acetylglutamate synthase
deficiency, ornithine translocase deficiency and
lysinuric protein intolerance, Well-established
use application (Article 10a of Directive No
2001/83/EC)

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

WPAR

**Restasis - ciclosporin -
EMA/H/C/004229**

Allergan Pharmaceuticals International Ltd, for
the treatment of moderate dry eye disease in
adults, Known active substance (Article 8(3) of
Directive No 2001/83/EC)

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

WPAR

**Rubraca - rucaparib - EMA/H/C/004272,
Orphan**

Clovis Oncology UK Ltd, treatment of ovarian
cancer, New active substance (Article 8(3) of

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

Directive No 2001/83/EC)

Zessly - infliximab - EMEA/H/C/004647
Sandoz GmbH, treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis, Similar biological application (Article 10(4) of Directive No 2001/83/EC)

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

B.5. TYPE II VARIATION, WORKSHARING PROCEDURE OUTCOMES

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

B.5.1. CHMP assessed procedures scope: Pharmaceutical aspects

Benepali - etanercept - EMEA/H/C/004007/II/0031/G
Samsung Bioepis UK Limited, Rapporteur: Andrea Laslop
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 22.02.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Dupixent - dupilumab - EMEA/H/C/004390/II/0002
sanofi-aventis groupe, Rapporteur: Jan Mueller-Berghaus
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 22.03.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Dupixent - dupilumab - EMEA/H/C/004390/II/0003/G
sanofi-aventis groupe, Rapporteur: Jan Mueller-Berghaus
Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

Eptifibatide Accord - eptifibatide - EMEA/H/C/004104/II/0003
Accord Healthcare Limited, Generic, Generic of Integrilin, Rapporteur: Jayne Crowe
Request for Supplementary Information adopted on 19.04.2018.

Request for supplementary information adopted with a specific timetable.

Eylea - aflibercept - EMEA/H/C/002392/II/0040/G
Bayer AG, Rapporteur: Alexandre Moreau
Opinion adopted on 19.04.2018.
Request for Supplementary Information adopted on 22.02.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

<p>Eylea - aflibercept - EMA/H/C/002392/II/0041/G Bayer AG, Rapporteur: Alexandre Moreau Opinion adopted on 19.04.2018. Request for Supplementary Information adopted on 22.02.2018.</p>	<p>Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Granupas - para-aminosalicylic acid - EMA/H/C/002709/II/0024, Orphan Lucane Pharma, Rapporteur: Greg Markey Opinion adopted on 26.04.2018.</p>	<p>Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Hemoblast - thrombin - EMA/H/D/002769/II/0003/G BSI Group, Rapporteur: Daniela Melchiorri Opinion adopted on 26.04.2018.</p>	<p>Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Hizentra - human normal immunoglobulin - EMA/H/C/002127/II/0093/G CSL Behring GmbH, Rapporteur: Jan Mueller-Berghaus Opinion adopted on 19.04.2018.</p>	<p>Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Imraldi - adalimumab - EMA/H/C/004279/II/0007/G Samsung Bioepis UK Limited (SBUK), Rapporteur: Outi Mäki-Ikola Opinion adopted on 26.04.2018.</p>	<p>Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Maviret - glecaprevir / pibrentasvir - EMA/H/C/004430/II/0006/G AbbVie Limited, Rapporteur: Joseph Emmerich Opinion adopted on 26.04.2018.</p>	<p>Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Mosquirix - plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - EMA/H/W/002300/II/0028 GlaxoSmithKline Biologicals SA, Rapporteur: Jan Mueller-Berghaus Opinion adopted on 12.04.2018.</p>	<p>Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>Naglazyme - galsulfase - EMA/H/C/000640/II/0070 BioMarin Europe Ltd, Rapporteur: Greg Markey Request for Supplementary Information adopted on 12.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>NexoBrid - concentrate of proteolytic enzymes enriched in bromelain - EMA/H/C/002246/II/0035, Orphan MediWound Germany GmbH, Rapporteur: Harald Enzmann Request for Supplementary Information adopted</p>	<p>Request for supplementary information adopted with a specific timetable.</p>

on 12.04.2018.

**NovoEight - turoctocog alfa -
EMA/H/C/002719/II/0021/G**

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

Opinion adopted on 19.04.2018.

Request for Supplementary Information adopted on 15.03.2018, 14.12.2017.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Ongentys - opicapone -
EMA/H/C/002790/II/0009**

Bial - Portela & C^a, S.A., Rapporteur: Greg Markey

Request for Supplementary Information adopted on 26.04.2018.

Request for supplementary information adopted with a specific timetable.

**Pegasys - peginterferon alfa-2a -
EMA/H/C/000395/II/0099/G**

Roche Registration GmbH, Rapporteur: Filip Josephson

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Pioglitazone Accord - pioglitazone -
EMA/H/C/002277/II/0015/G**

Accord Healthcare Limited, Generic, Generic of Actos, Rapporteur: Peter Kiely

Opinion adopted on 19.04.2018.

Request for Supplementary Information adopted on 15.03.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Taltz - ixekizumab -
EMA/H/C/003943/II/0014**

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

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 15.03.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Trulicity - dulaglutide -
EMA/H/C/002825/II/0026**

Eli Lilly Nederland B.V., Rapporteur: Greg Markey

Opinion adopted on 19.04.2018.

Request for Supplementary Information adopted on 15.03.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Vaniqa - eflornithine -
EMA/H/C/000325/II/0051**

Almirall S.A, Rapporteur: Peter Kiely

Request for Supplementary Information adopted

Request for supplementary information adopted with a specific timetable.

on 26.04.2018, 22.03.2018, 26.10.2017.

**Zerbaxa - ceftolozane / tazobactam -
EMA/H/C/003772/II/0015/G**

Merck Sharp & Dohme Limited, Rapporteur:
Robert James Hemmings

Request for Supplementary Information adopted
on 26.04.2018.

Request for supplementary information adopted
with a specific timetable.

WS1177/G

Neulasta-

EMA/H/C/000420/WS1177/0097/G

Ristempa (SRD)-

EMA/H/C/003910/WS1177/0012/G

Amgen Europe B.V., Lead Rapporteur: Robert
James Hemmings

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted
on 25.01.2018, 14.09.2017.

Positive Opinion adopted by consensus on
26.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

WS1281/G

Hexacima-

EMA/H/C/002702/WS1281/0072/G

Hexaxim-

EMA/H/W/002495/WS1281/0077/G

Hexyon-

EMA/H/C/002796/WS1281/0076/G

Sanofi Pasteur, Lead Rapporteur: Jan Mueller-
Berghaus

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted
on 25.01.2018.

Positive Opinion adopted by consensus on
12.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

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

Abraxane - paclitaxel -

EMA/H/C/000778/II/0087

Celgene Europe Limited, Rapporteur: Paula
Boudewina van Hennik, "Update of section 4.8
of the SmPC in order to include the warning
tumour lysis syndrome following a safety
cumulative review of this signal. In addition, the
marketing authorisation holder took the
opportunity to update the wording on section
4.6 to introduce additional recommendation to
perform a pregnancy test prior treatment with
paclitaxel. The package leaflet has been
updated accordingly."

Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on
12.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

**Bexsero - meningococcal group b vaccine
(recombinant, component, adsorbed) -**

Positive Opinion adopted by consensus on
26.04.2018. The Icelandic and Norwegian CHMP

EMEA/H/C/002333/II/0059

GSK Vaccines S.r.l, Rapporteur: Kristina Dunder, "Update of section 4.2 of the SmPC to update the dosing schedule for infants aged 3 months to 5 months and aged 2 years to 10 years based on the results from studies V72_28 and V72_28E1.
Update of section 4.8 of the SmPC to include the number of subjects exposed to at least 1 dose based on the results from studies V72_28 and V72_28E1.
Update of section 5.1 of the SmPC to update the information about immunogenicity in infants and children based on the results from studies V72_28 and V72_28E1.
The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the product information and Annex A and also to update the list of local representatives in the package leaflet. Furthermore, Bexsero is removed from the additional monitoring list and consequently the inverted black triangle is deleted from the SmPC and package leaflet."
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 22.02.2018, 12.10.2017.

Members were in agreement with the CHMP recommendation.

Celsentri - maraviroc -**EMEA/H/C/000811/II/0054/G**

ViiV Healthcare UK Limited, Rapporteur: Filip Josephson, "Update of sections 4.5 and 5.2 of the SmPC in order to update the data regarding drug metabolising enzymes and drug transporters from several completed in vitro studies and to support the addition of pharmacogenomic information based on final results from study (A4001110), respectively. Furthermore, section 5.1 has been updated with information on genotypic resistance. Additionally, minor changes have been introduced in 4.2, 4.4, and 5.1 sections of the SmPC. The Package Leaflet section on How to measure the dose and take the medicine has been updated to further clarify the instructions."
Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Daklinza - daclatasvir -**EMEA/H/C/003768/II/0028**

Bristol-Myers Squibb Pharma EEIG, Rapporteur: Filip Josephson, "Submission of the final report from study A1444379. This is an interventional

Request for supplementary information adopted with a specific timetable.

open-label phase 3 study evaluating daclatasvir and sofosbuvir with ribavirin in cirrhotic subjects with genotype 3 chronic hepatitis C infection to demonstrate the sustained virologic response at follow-up Week 12 (SVR12) rate, defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantification (LLOQ) target detected (TD) or target not detected (TND) at follow-up Week 12 in subjects treated with 24 weeks of daclatasvir (DCV) + sofosbuvir (SOF) + ribavirin (RBV) therapy was greater than the historical threshold sustained virologic response (SVR) rate.”

Request for Supplementary Information adopted on 12.04.2018.

**Humira - adalimumab -
EMA/H/C/000481/II/0172**

AbbVie Deutschland GmbH & Co. KG,
Rapporteur: Kristina Dunder, “Update of sections 5.1 and 5.2 of the SmPC for 40mg/0.8ml and 40mg/0.4 ml Prefilled pen and prefilled syringe in order to add information on non-radiographic axial spondyloarthritis following final results from Humira remission-withdrawal-retreatment study (M13-375) listed in the RMP.”

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 01.02.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Infanrix hexa - diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) - EMA/H/C/000296/II/0235

GlaxoSmithkline Biologicals SA, Rapporteur: Bart Van der Schueren, “Update of section 4.5 of the SmPC in order to update the interactions section with additional data on the co-administration with Meningococcal serogroup B vaccine (MenB) in order to facilitate the administration of Infanrix hexa and Bexsero to infants and toddlers based on final results from clinical studies V72P12, V72P13 and V72P16.”

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 08.02.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Isentress - raltegravir -
EMA/H/C/000860/II/0073**

Request for supplementary information adopted with a specific timetable.

Merck Sharp & Dohme Limited, Rapporteur:
Greg Markey, "Update of sections 4.6 and 5.3 of the SmPC, upon request by PRAC following the assessment of the latest PSUR (PSUSA/00010373/201703), to include revised safety information about pregnancy and risk of malformative or foetal toxicity (LEG). The Package Leaflet has been updated accordingly." Request for Supplementary Information adopted on 12.04.2018.

Jinarc - tolvaptan -

EMA/H/C/002788/II/0010

Otsuka Pharmaceutical Europe Ltd, Rapporteur:
Greg Markey, "Submission of the final report from a completed PK study (156-14-216, a Phase 1, Single centre, Open-label, drug interaction trial to Investigate the Effect of Oral Flucomazole, a Moderate CYP3A4 Inhibitor, on Tolvaptan Pharmacokinetic in Healthy Adult Subjects - MEA 003)." Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Kyprolis - carfilzomib -

EMA/H/C/003790/II/0025, Orphan

Amgen Europe B.V., Rapporteur: Jorge Camarero Jiménez, "Update of sections 4.8 and 5.1 of the SmPC based on the final analysis of overall survival data from study PX-171-009 (ASPIRE): a randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) vs lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma. Section 4.8 of the SmPC is updated to add "Clostridium difficile colitis" as new adverse reaction with frequency uncommon, to change the frequency for "Myocardial infarction" from uncommon to common and to add minor updates of figures in some adverse reactions from subsection "Description of selected adverse reactions": cardiac failure, myocardial infarction, hypertension and venous thromboembolic events. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include editorial changes and bring the PI in line with the latest QRD template version 10." Opinion adopted on 26.04.2018. Request for Supplementary Information adopted on 22.03.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Lumigan - bimatoprost -
EMA/H/C/000391/II/0055**

Allergan Pharmaceuticals Ireland, Rapporteur: Mark Ainsworth, "Submission of the final report of the Phase 4 clinical safety study P-192024-054 to evaluate the long-term safety of Lumigan 0.1 mg/ml compared with Lumigan 0.3 mg/ml and listed as a category 3 study in the RMP."
Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**MabThera - rituximab -
EMA/H/C/000165/II/0143**

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, "Update of section 5.1 of the SmPC to reflect the final results of the PRIMA study (MO18264), a study in Patients with Advanced Follicular Lymphoma Evaluating the Benefit of Maintenance Therapy with Rituximab after Induction of Response with Chemotherapy plus Rituximab in Comparison with No Maintenance Therapy."
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 15.03.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Mirvaso - brimonidine -
EMA/H/C/002642/II/0017**

Galderma International, Rapporteur: Filip Josephson, "Update of section 4.8 of the SmPC in order to update the frequency of the adverse drug reaction (ADR) rosacea from "uncommon" to "common" following a re-examination of the frequency of ADRs in pertinent studies. The package leaflet is updated accordingly."
Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**NovoRapid - insulin aspart -
EMA/H/C/000258/II/0121**

Novo Nordisk A/S, Rapporteur: Kristina Dunder, "Update of section 4.2 of the SmPC to include a passive discouragement of withdrawing insulin with a syringe from cartridges and pre-filled pens; update of section 6.6 of the SmPC not to allow the withdrawal of insulin with a syringe from cartridges and pre-filled pens in emergency situations. This variation was submitted to fulfil a recommendation by the PRAC in November 2017, subsequent to the evaluation of the signal on potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia. The PL is

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

updated accordingly. In addition, the MAH took the opportunity to reinsert and clarify information in the SmPC regarding mixing of NovoRapid with NPH insulin (sections 4.2 and 6.2), which has previously been deleted from the SmPC by mistake. Other editorial changes are also proposed within this variation. Moreover, Annex A is updated to reflect that only the vial is to be used intravenously.”
Opinion adopted on 26.04.2018.

**Pradaxa - dabigatran etexilate -
EMA/H/C/000829/II/0108**

Boehringer Ingelheim International GmbH,
Rapporteur: Mark Ainsworth, “Update of sections 4.2, 4.4. and 5.1 of the SmPC for Pradaxa 110 and 150 mg for the stroke prevention in atrial fibrillation, deep vein thrombosis and pulmonary embolism indications based on the results from study 1160.186: `A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110 mg and 150 mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0-3.0) plus clopidogrel or ticagrelor and aspirin in patients with non-valvular atrial fibrillation that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI)’In addition, the MAH took the opportunity to correct in section 4.3 a contraindication that refers to concomitant treatment with heparin, based on the data assessed in the context of variation II/103 to reflect the fact that heparin is administered during ablation procedure at the same time as dabigatran etexilate. Section 4.5 is similarly updated. Section 4.8 is updated with a minor re-wording.”

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Pradaxa - dabigatran etexilate -
EMA/H/C/000829/II/0111**

Boehringer Ingelheim International GmbH,
Rapporteur: Mark Ainsworth, PRAC Rapporteur: Doris Stenver, “Update of section 5.1 of the SmPC to reflect the phase II outcome results from the Global Registry on Long-Term Oral Antithrombotic Treatment In Patients with Atrial Fibrillation (GLORIA-AF) including the

Request for supplementary information adopted with a specific timetable.

main objective "to collect real-world data on important outcome events of antithrombotic treatments for the prevention of stroke" for patients taking pradaxa. In addition, the results of the Medicare study (P14-15648) are proposed to be included also in section 5.1 with further information on the effectiveness and safety of pradaxa in patients with NVAf (non-valvular atrial fibrillation) in a real-world setting.

The RMP (version 35.0) has also been updated to reflect the study results."

Request for Supplementary Information adopted on 26.04.2018.

**Praluent - alirocumab -
EMA/H/C/003882/II/0036**

sanofi-aventis groupe, Rapporteur: Johann Lodewijk Hillege, "Submission of the clinical study report of study LTS13463 (Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732, & LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia) as per MEA010." Opinion adopted on 19.04.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Praluent - alirocumab -
EMA/H/C/003882/II/0037**

sanofi-aventis groupe, Rapporteur: Johann Lodewijk Hillege, "Submission of the second step analysis report of the clinical study EFC13786 (study title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Alirocumab in Patients with Primary Hypercholesterolemia not treated with a statin) as per MEA014." Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Remicade - infliximab -
EMA/H/C/000240/II/0212**

Janssen Biologics B.V., Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wandel Liminga, "Update of section 4.4 to include a warning recommending adult patients to be brought up to date with all vaccinations if possible prior to initiating Remicade therapy (in line with the current warning for children) and to clarify that patients on infliximab may receive concurrent vaccinations, except for live vaccines. Relevant sections of the PL and the RMP (v 15.1) were updated accordingly.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

The MAH took the opportunity to include minor editorial changes in the PI.”
Opinion adopted on 26.04.2018.

Remicade - infliximab -

EMA/H/C/000240/II/0213/G

Janssen Biologics B.V., Rapporteur: Kristina Dunder, “Update of section 4.8 of the SmPC in order to add the following adverse reactions: ‘Hemophagocytic Lymphohistiocytosis (HLH)’ with a frequency ‘very rare’ and ‘Linear IgA Bullous Dermatitis (LABD)’ with a ‘rare’ frequency. In addition, the Marketing authorisation holder (MAH) took the opportunity to add additional instructions for obese Adult patients in section 6.6 of the SmPC; relevant sections of the PL have been updated accordingly. The MAH also took the opportunity to introduce some editorial changes in the Product Information.”
Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Revlimid - lenalidomide -

EMA/H/C/000717/II/0097, Orphan

Celgene Europe Limited, Rapporteur: Alexandre Moreau, “Update of the SmPC section 4.8 to include solid organ transplant rejection as an adverse reaction (ADR) with the frequency not known in line with the Company Core Data Sheet (CCDS). The MAH also took the opportunity to further align the SmPC section 4.8 with the CCDS by adding the following ADRs reported as serious in some clinical trials: cellulitis, hypercalcaemia, and musculoskeletal and connective tissue pain and discomfort (including back pain). Minor editorial changes have been introduced throughout the PI. The Package leaflet has been updated accordingly.”
Opinion adopted on 19.04.2018.
Request for Supplementary Information adopted on 15.02.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

SonoVue - sulphur hexafluoride -

EMA/H/C/000303/II/0037/G

Bracco International B.V., Rapporteur: Alexandre Moreau, “Grouped variation application in order to align with Company Core Data Sheet (CCDS):
Update of section 4.4 of the SmPC in order to reword the warning on hypersensitivity reactions.
Update of section 4.4 of the SmPC in order to

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

reword the warning for patients with unstable cardiopulmonary status

Update of section 4.4 of the SmPC in order to delete the warning for patients on mechanical ventilation or with unstable neurological diseases

Update of section 4.4 of the SmPC in order to delete the warning for patients with clinically significant pulmonary disease, including severe chronic obstructive pulmonary disease

Update of section 4.8 of the SmPC in order to revise the table of Adverse Drug Reactions. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes/corrections in sections 4.8 and 4.9 of the SmPC.”

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018.

Spinraza - nusinersen - EMEA/H/C/004312/II/0004, Orphan

Biogen Idec Ltd, Rapporteur: Bruno Sepodes, PRAC Rapporteur: Qun-Ying Yue, “Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The PIL and the RMP (new version 7.0) are proposed to be updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC”

Request for Supplementary Information adopted on 12.04.2018, 08.02.2018.

Request for supplementary information adopted with a specific timetable.

Starlix - nateglinide - EMEA/H/C/000335/II/0033

Novartis Europharm Limited, Rapporteur: Greg Markey, “Update of section 5.2 of the SmPC to add information on the accumulation of M1 metabolite in diabetic patients with end-stage renal disease (ESRD), based on the review of the Core Data Sheet. This information is reflected in section 4.4 of the SmPC. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with QRD template 10, combine the three SmPC into a single SmPC, align sections 1 and 2 of the package leaflet with the SmPC, and correct the name of the local representatives for Latvia and Bulgaria.”

Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Request for Supplementary Information adopted on 22.03.2018, 07.12.2017.

Taltz - ixekizumab -

EMA/H/C/003943/II/0016

Eli Lilly Nederland B.V., Rapporteur: Kristina Dunder, "Update section 5.1 of the SmPC to include the results of study RHBS (a Phase 3b, multicenter, randomised, double blind, double dummy, active comparator, and parallel group study of the efficacy and safety of ixekizumab versus ustekinumab for the treatment of moderate to severe psoriasis). The MAH took the opportunity to introduce minor typographical amendments in the product information."

Opinion adopted on 19.04.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Trulicity - dulaglutide -

EMA/H/C/002825/II/0025

Eli Lilly Nederland B.V., Rapporteur: Greg Markey, "Update of sections 4.2 and 5.1 of the SmPC to reflect the use of dulaglutide in Type 2 Diabetes Mellitus patients as add-on to sodium-glucose co-transporter 2 inhibitors (SGLT2i) therapy following completion of a study that investigated the effect of once weekly dulaglutide 1.5 mg or 0.75 mg added to SGLT2is, with or without concomitant use of metformin, on glycemic control and safety over a 24-weeks in patients with inadequately controlled T2DM (Study H9X-MC-GBGE (GBGE)).

The Package Leaflet is updated accordingly."

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

XALKORI - crizotinib -

EMA/H/C/002489/II/0054

Pfizer Limited, Rapporteur: Alexandre Moreau, "Update of section 5.1 of the SmPC to reflect the final analysis of overall survival (OS), a secondary endpoint, in Study A8081014, a randomized phase 3 trial comparing oral crizotinib to first line chemotherapy in patients with ALK-positive advanced non-squamous non-small cell lung cancer (NSCLC)."

Request for Supplementary Information adopted on 19.04.2018.

Request for supplementary information adopted with a specific timetable.

Xeljanz - tofacitinib -

EMA/H/C/004214/II/0008

Request for supplementary information adopted with a specific timetable.

Pfizer Limited, Rapporteur: Robert James Hemmings, "Submission of the final CSR for study A3921187 described in Part IV of the RMP. Study A3921187 is a phase 3b/4 randomized double-blind study of 5 mg of Tofacitinib with and without methotrexate in comparison to adalimumab with methotrexate in subjects with moderately to severely active rheumatoid arthritis."
Request for Supplementary Information adopted on 19.04.2018.

**Xeljanz - tofacitinib -
EMA/H/C/004214/II/0010**

Pfizer Limited, Rapporteur: Robert James Hemmings, "To update sections 4.4 and 4.8 of the SmPC and PIL to add a warning on Hypersensitivity and to add drug hypersensitivity, angioedema, and urticaria as ADRs with frequency not known, following a PRAC signal recommendation.
The Package Leaflet is updated accordingly."
Opinion adopted on 19.04.2018.

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Xeljanz - tofacitinib -
EMA/H/C/004214/II/0011**

Pfizer Limited, Rapporteur: Robert James Hemmings, "To update section 4.4 of the SmPC to indicate that post-marketing cases of HB reactivation have been reported following routine pharmacovigilance review."
Request for Supplementary Information adopted on 19.04.2018.

Request for supplementary information adopted with a specific timetable.

**Xydalba - dalbavancin -
EMA/H/C/002840/II/0021**

Allergan Pharmaceuticals International Ltd, Rapporteur: Filip Josephson, "Update to sections 4.4 and 4.8 of the product information in order to include back-pain as a symptom of infusion-related reactions in alignment with the last version Company Core Data Sheet (CCDS).

In addition, the MAH took the opportunity to add a precautionary statement to Section 6.6 to include flushing of the intravenous lines before and after dalbavancin infusion, to bring the PI in line with the latest QRD template version 10 and to update the local representatives in the PL"

Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

**Zavicefta - ceftazidime / avibactam -
EMA/H/C/004027/II/0009**

Pfizer Ireland Pharmaceuticals, Rapporteur:
Robert James Hemmings, "Update of sections 4.2 and 4.8 of the SmPC in order to reflect the availability of final CSR for the paediatric study C3591004 (D4280C00015). Study D4280C00015 is a single blind, randomised, multi-centre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs). In addition, the MAH has updated the sodium statements in the SmPC (section 4.4) and Package Leaflet to align with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The legal status 'medicinal product subject to medical prescription' is proposed to be removed from Annex IIIA, as per the QRD template. Moreover, the MAH is introducing a correction in the Polish annexes (from ZAVICEFTA 2 g + 0.5g to ZAVICEFTA 2 g/0.5g)."
Request for Supplementary Information adopted on 19.04.2018.

Request for supplementary information adopted with a specific timetable.

**WS1298
Enurev Breezhaler-
EMA/H/C/002691/WS1298/0024
Seebri Breezhaler-
EMA/H/C/002430/WS1298/0024
Tovanor Breezhaler-
EMA/H/C/002690/WS1298/0027**

Novartis Europharm Limited, Lead Rapporteur:
Mark Ainsworth, "Submission of the final study report of the Post-Authorisation Efficacy Study (PAES) to compare the efficacy, safety and tolerability of glycopyrronium given at a dose of 44 µg QD and 22 µg BID in patients with stable COPD and moderate to severe airflow obstruction."
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted on 15.02.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**WS1307
OFEV-EMA/H/C/003821/WS1307/0019
Vargatef-**

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

EMEA/H/C/002569/WS1307/0019

recommendation.

Boehringer Ingelheim International GmbH, Lead Rapporteur: Sinan B. Sarac, "Update of section 4.4 of the SmPC for Ofev and Vargatef to amend the current warning on drug induced liver injury based one case of severe liver injury with fatal outcome reported for Ofev during the post-marketing phase. In addition section 4.4 of the Ofev SmPC is updated to include when the majority of the hepatic events occurred and on the need for hepatic transaminases and bilirubin levels to be measured at regular intervals during the first 3 months of treatment. Section 4.8 of the Vargatef SmPC is also updated to include in the summary of the safety profile that the safety data is also based on post-marketing data. The Package Leaflet is updated accordingly. The MAH is proposing to distribute a DHPC for Ofev. In addition, the Worksharing applicant (WSA) took the opportunity to make some corrections to the Bulgarian, Estonian, Icelandic, Latvian and Maltese translations for Ofev and Bulgarian, Estonian, Latvian and Maltese translations for Vargatef."

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 25.01.2018.

WS1348

Request for supplementary information adopted with a specific timetable.

**Exviera-EMEA/H/C/003837/WS1348/0035
Viekirax-****EMEA/H/C/003839/WS1348/0042**

AbbVie Limited, Lead Rapporteur: Filip Josephson, "Submission of the final report from study (M14-227) listed as a category 3 study in the RMP. This is a Phase 3b study designed to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir in HCV infected patients with Child-Pugh B decompensated cirrhosis."

Request for Supplementary Information adopted on 12.04.2018.

WS1356/G

Request for supplementary information adopted with a specific timetable.

Humalog-**EMEA/H/C/000088/WS1356/0163/G****Liprolog-****EMEA/H/C/000393/WS1356/0125/G**

Eli Lilly Nederland B.V., Lead Rapporteur: Robert James Hemmings, "C.I.4: Update of sections 4.2 and 6.6 of the SmPC of Humalog/Liprolog in cartridges following the

signal PRAC recommendation (EPITT 18893);
the Package Leaflet and Labelling are updated.

B.II.e.5.b: To delete the BASAL presentations:
EU/1/96/007/010, 029, 037 and 038 for
Humalog Basal and EU/1/01/195/022, 023, 026
and 027 for Liprolog Basal.

In addition, the Worksharing applicant (WSA)
took the opportunity to combine all SmPCs
resulting in four SmPCs: 100 units/ml
presentations, Mix 25 100 units/ml
presentations, Mix50 100 units/ml presentations
and 200 units/ml presentations. The MAH also
brought the product information in line with the
latest QRD template version 10, 02/2016. Minor
editorial changes have been included.”
Request for Supplementary Information adopted
on 12.04.2018.

B.5.3. CHMP-PRAC assessed procedures

Advate - octocog alfa -

EMA/H/C/000520/II/0091

Baxter AG, Rapporteur: Jan Mueller-Berghaus,
PRAC Rapporteur: Brigitte Keller-Stanislawski,
“Update of section 4.2 of the SmPC in order to
remove a statement that the use of 2 ml
presentations has not been documented for
paediatric subjects below 2 years of age. This
update follows final results from study O61101
listed as a category 3 study in the RMP; this was
a prospective, non-interventional, post-
marketing surveillance study that assessed the
safety and efficacy of Advate reconstituted in 2
ml of sterile water for injection during routine
clinical practice in the EU.

The Package Leaflet is updated accordingly. The
RMP version 15.1 has also been submitted.”

Request for Supplementary Information adopted
on 12.04.2018.

Request for supplementary information adopted
with a specific timetable.

Alecensa - alectinib -

EMA/H/C/004164/II/0010

Roche Registration GmbH, Rapporteur: Filip
Josephson, PRAC Rapporteur: Patrick Batty,
“Update of sections 4.2 and 5.2 of the SmPC in
order to update information on the effect of
hepatic impairment on the pharmacokinetics of
alectinib based on final results from study
NP29783. The Package Leaflet is updated
accordingly. The RMP has also been updated to

Positive Opinion adopted by consensus on
26.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

version 3.0. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest EC guidance regarding warning statements on sodium.”

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018.

**Caprelsa - vandetanib -
EMA/H/C/002315/II/0028**

Genzyme Europe BV, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni, “Update of sections 4.1, 4.4 and 5.1 of the SmPC in order to delete the information regarding Rearranged during Transfection (RET) mutation. The application addresses SOB 001 and the MAH proposes to revert from conditional marketing authorisation to standard marketing authorisation. Annex II and Package Leaflet are updated accordingly. The RMP version 12.2 has also been submitted.

In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.”

Request for Supplementary Information adopted on 26.04.2018, 14.12.2017.

Request for supplementary information adopted with a specific timetable.

**Cerdelga - eliglustat -
EMA/H/C/003724/II/0015/G, Orphan**

Genzyme Europe BV, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Dolores Montero Corominas, “Update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC based on the final results from studies POP13777 “pharmacokinetics of oral single-dose eliglustat in subjects with hepatic impairment” (MEA003.3) and POP13778 “pharmacokinetics of oral single-dose eliglustat in subjects with renal impairment” (MEA004.3). Consequentially, the additional risk minimisation measures in annex II D of the product information have been amended. The Package Leaflet is updated accordingly. The RMP version 5.1 is accepted.”

Opinion adopted on 26.04.2018.

Request for Supplementary Information adopted on 22.02.2018, 14.12.2017.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

**Defitelio - defibrotide -
EMA/H/C/002393/II/0026, Orphan**

Genzyme S.r.l., Rapporteur: Nithyanandan Nagercoil, PRAC Rapporteur: Julie Williams,

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

“Update of sections 4.8 and 5.1 of the SmPC in order to update the frequencies of adverse reactions included in the tabulated list of adverse reactions and to update the clinical efficacy and safety information based on the results from study 2006-05 listed as category 3 in the risk management plan (RMP). This is a phase 3, open-label expanded access study designed to provide access to defibrotide as an investigational new drug to patients with severe hepatic veno-occlusive disease. The final study report has been submitted. The RMP (version 3.4) and package leaflet are updated accordingly. In addition, the MAH took the opportunity to bring the SmPC in line with the latest QRD template (version 10), to update the list of local representatives in the package leaflet and to correct a translation error in the Polish, Finnish, Danish and Latvian languages.”
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted on 08.02.2018, 30.11.2017, 28.09.2017.

recommendation.

Defitelio - defibrotide -

EMA/H/C/002393/II/0027, Orphan

Gentium S.r.l., Rapporteur: Nithyanandan Nagercoil, PRAC Rapporteur: Julie Williams, “Submission of an updated RMP version 4.0 in order to re-classify the imposed non-interventional PASS listed as a category 2 study in the RMP (specific obligation) to a study listed as a category 3 in the RMP (required additional pharmacovigilance activities). This study is an observational registry (DF-VOD2013-03-REG) which aims to record safety and outcome data in patients diagnosed with severe VOD following HSCT treated or not with defitelio. The Annex II of the product information is updated accordingly.”

Request for Supplementary Information adopted on 26.04.2018, 22.02.2018, 09.11.2017.

Request for supplementary information adopted with a specific timetable.

Eliquis - apixaban -

EMA/H/C/002148/II/0050

Bristol-Myers Squibb / Pfizer EEIG, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Menno van der Elst, “Update of sections 4.2 and 5.1 of the SmPC in order to update the posology, efficacy and safety information for patients undergoing cardioversion based on the final results from the post-authorisation efficacy study EMANATE. The package leaflet and the

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

RMP (version 19.0) are updated accordingly. In addition, the marketing authorisation holder (MAH) took the opportunity to update their address in the product information and the list of local representative in the package leaflet.”
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 25.01.2018.

Keppra - levetiracetam -

EMA/H/C/000277/II/0169/G

UCB Pharma S.A., Rapporteur: Koenraad Norga, PRAC Rapporteur: Laurence de Fays, “1) Update of section 4.8 of the SmPC to add the ADR Gait Disturbance, to address the CHMP recommendations from P46/085;
2) Update of section 4.2 of the SmPC to add Dysgeusia as a potential experience post administration;
3) Update of Section 4.6 to add information on 'Women of childbearing potential' and to update the Pregnancy section, to address PRAC recommendations from LEG-084.1;
The Package Leaflet is updated accordingly.
An updated to the Risk Management Plan (version 8.1) is included to address PRAC recommendations from LEG 84.1.”
Opinion adopted on 26.04.2018.
Request for Supplementary Information adopted on 22.03.2018, 25.01.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Kuvan - sapropterin -

EMA/H/C/000943/II/0052, Orphan

BioMarin International Limited, Rapporteur: Peter Kiely, PRAC Rapporteur: Almath Spooner, “Based on a review of the post-marketing experience and in order to harmonise the safety information with the CCDS, update of section 4.8 of the Kuvan SmPC to add the following adverse events regarding gastrointestinal tract: dyspepsia, nausea and gastritis. The Package Leaflet is updated accordingly.
In addition, the MAH took the opportunity to implement the latest QRD template and bring up to date sections 17 and 18 of Annex IIIA.”
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted on 30.11.2017.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

OPDIVO - nivolumab -

EMA/H/C/003985/II/0047

Bristol-Myers Squibb Pharma EEIG, Rapporteur:

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

<p>Jorge Camarero Jiménez, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on the nivolumab use in patients who have previously undergone allogeneic HSCT and the increased risk of rapid onset and severe Graft versus Host Disease (GVHD) based on evidence from spontaneous case reports, literature case reports, and from 2 multicenter case series. Annex II.D and the Package Leaflet are updated accordingly. The RMP version 10.2 has also been submitted to include the "risk of GVHD with nivolumab after allogeneic HSCT" as an "Important Potential Risk" based on the RMP template (Revision 2). In addition, the Marketing authorisation holder (MAH) took the opportunity to make some minor editorial corrections to the PI." Opinion adopted on 26.04.2018. Request for Supplementary Information adopted on 22.03.2018.</p>	<p>recommendation.</p>
<p>Prevenar 13 - pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - EMEA/H/C/001104/II/0161 Pfizer Limited, Rapporteur: Kristina Dunder, PRAC Rapporteur: Qun-Ying Yue, "Submission of the final study report from study B1851041, a phase 4 post marketing study to determine ' National trends in Ambulatory Care Visits for Otitis Media in Children Under the Age of Five in the United States.' Consequently, the RMP version 12 has been updated." Request for Supplementary Information adopted on 12.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>Privigen - human normal immunoglobulin - EMEA/H/C/000831/II/0129 CSL Behring GmbH, Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Brigitte Keller-Stanislawski, "Update of section 4.3 of the SmPC to remove the hyperprolineamia contraindication. The package leaflet and RMP (version 6.0) are updated accordingly." Request for Supplementary Information adopted on 12.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>Revlimid - lenalidomide - EMEA/H/C/000717/II/0098, Orphan</p>	<p>Request for supplementary information adopted with a specific timetable.</p>

Celgene Europe Limited, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni, "Update of the Annex II key elements of the risk minimisation programme with information on prescription duration and to revise due dates of the PASS CC-5013-MDS-10 and 12. The section 4.4 of the SmPC has been updated accordingly. Furthermore, the RMP version 35 has been revised in line with the updated Guideline on Good Pharmacovigilance Practices (GVP) Module V to propose the reclassification and/or renaming of known safety concerns associated with the use of lenalidomide. Consequently, Annex IID has been updated accordingly." Request for Supplementary Information adopted on 12.04.2018.

Rydapt - midostaurin -

EMA/H/C/004095/11/0002, Orphan

Novartis Europharm Limited, Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva, "Update of sections 4.5 and 5.2 of the SmPC in order to reflect the results from study R1600721 "Assessment of PKC412 and its metabolites (CGP052421 and CGP062221) as inhibitors of human bile salt export pump (BSEP) " and study R1701192 'In vitro assessment of cytochrome P450 3A4 and 3A5 enzyme inhibition by PKC412, CGP52421 and CGP62221', in fulfilment of the post-authorisation measures MEA 011 and REC 014. In addition, the MAH took the opportunity to update section 5.2 to correct figures as per Study A2107-Amendment 02 already assessed and to make editorial changes in the SmPC. The RMP (v 2.0) has also been updated to reflect the study results. In addition, the search criteria for the important identified risk pulmonary toxicity (including pleural effusion and interstitial lung disease) was updated to include the PT-pleural effusion." Opinion adopted on 26.04.2018. Request for Supplementary Information adopted on 22.03.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Stribild - elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil -
EMA/H/C/002574/11/0087

Gilead Sciences International Limited, Rapporteur: Robert James Hemmings, PRAC Rapporteur: Julie Williams, "Submission of the

Request for supplementary information adopted with a specific timetable.

final study report for Study GS-EU-236-0141, listed as a category 3 study in the Risk Management Plan, in order to fulfil a post-authorisation measure (PAM) MEA 006 for Stribild; This study is an Observational Drug Utilization Study of Stribild in Adults with HIV-1 Infection

With this application and as agreed with the EMA, Gilead is also taking this opportunity to address the outstanding questions from MEA 002.3.”

Request for Supplementary Information adopted on 12.04.2018, 11.01.2018.

SYLVANT - siltuximab - EMEA/H/C/003708/II/0026/G, Orphan

Janssen-Cilag International NV, Rapporteur: Concepcion Prieto Yerro, PRAC Rapporteur: Brigitte Keller-Stanislawski, “Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the product information following final results from studies CNTO328MCD2001 and CNTO328MCD2002 listed as imposed obligation in the Annex II (ANX002 and ANX003). The Package Leaflet are updated accordingly. The RMP version 4.0 has also been submitted. In addition, the list of local representatives (Czech Republic, Lithuania and Portugal) in the PL is being revised”

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 30.11.2017.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Symtuza - darunavir / cobicistat / emtricitabine / tenofovir alafenamide - EMEA/H/C/004391/II/0003/G

Janssen-Cilag International N.V., Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Julie Williams, “Update of sections 4.8 and 5.1 of the SmPC in order to reflect the week-48 results from 2 studies (TMC114FD2HTX3001 and TMC114IFD3013) listed as category 3 studies in the RMP; these are phase 3 studies to evaluate the efficacy and safety of D/C/F/TAF once daily fixed-dose combination regimen versus a regimen consisting of DRV/COBI FDC co-administered with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected subjects (study TMC114FD2HTX3001) and to evaluate switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects (study TMC114IFD3013). The RMP version 2.2 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to make minor editorial revision in the product information."

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 08.02.2018.

**Tecentriq - atezolizumab -
EMA/H/C/004143/II/0004**

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva, "Update of section 4.8 of the SmPC in order to update the safety information based on the primary results from study IMvigor211 in order to fulfil ANX 002 (the submission of the final CSR being listed as an imposed PAES in Annex II.D). This is a phase III, open-label, multicentre, randomized study to investigate the efficacy and safety of atezolizumab (anti- PD-L1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy. The Package Leaflet and the RMP (version 3.0, according to GVP module V revision 2) are updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to implement some editorial changes throughout the Product Information." Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

**XGEVA - denosumab -
EMA/H/C/002173/II/0059**

Amgen Europe B.V., Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, "Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information and to revise the special warnings, precautions for use and undesirable effects based on cases of clinically significant hypercalcemia following discontinuation of denosumab in patients with growing skeletons (i.e., adolescent subject with giant-cell tumour of bone (GCTB) in Study 20062004) and in postmarketing reports of pediatric patients treated with denosumab for

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

GCTB or for unapproved indications was previously determined to be an important identified risk ; the Package Leaflet are is updated accordingly. Consequently the RMP revised version 32 has also been submitted.”

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 08.03.2018.

**Yervoy - ipilimumab -
EMA/H/C/002213/II/0054**

Bristol-Myers Squibb Pharma EEIG, Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Sabine Straus, “Update of section 5.1 of the SmPC to update the overall survival data of ipilimumab 3mg/kg monotherapy pooled across studies based on the final results of study CA184332 and CA184338 listed as category 3 studies in the RMP, in order to fulfil MEA 035 and MEA 030.1 respectively. Study CA184332 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy in a community practice setting and study CA184438 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy. The RMP version 18.4 has also been submitted.”

Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

**WS1335
Rixathon-
EMA/H/C/003903/WS1335/0010
Riximyo-**

EMA/H/C/004729/WS1335/0010
Sandoz GmbH, Lead Rapporteur: Jan Mueller-Berghaus, Lead PRAC Rapporteur: Doris Stenver, “Submission of final study reports for studies GP13-302 (a randomized, double-blind, parallel-group safety study with the aim to specifically address a potential safety risk of a switch from treatment with originator rituximab (Mabthera/Rituxan) to treatment with GP2013) and GP13-201 (a 52-week multicenter, randomized, double-blind, parallel-arm, comparative study in patients with active Rheumatoid Arthritis (RA) refractory or intolerant to standard DMARDs and one or up to three anti-TNFs therapies). The RMP (version 3.0) has been updated accordingly.”

Request for supplementary information adopted with a specific timetable.

Request for Supplementary Information adopted on 12.04.2018.

WS1343
Relvar Ellipta-
EMA/H/C/002673/WS1343/0036

Revinty Ellipta-
EMA/H/C/002745/WS1343/0032

Glaxo Group Ltd, Lead Rapporteur: Concepcion Prieto Yerro, Lead PRAC Rapporteur: Dolores Montero Corominas, "C.I.11.b) Submission of an updated RMP version 9.2 to reflect the addition of information with regards SLS-asthma completion (HZA115150- interventional post-authorisation safety Category 1 study to further investigate the risk of pneumonia-ANX005), to update the important identified risk of pneumonia with regards findings from the study, and to provide a justification for removal of the important potential risk of asthma related intubations and deaths and a justification for removal of missing information related to long term use in asthma (>1 year). Consequently Annex II condition of the product information is updated accordingly."

Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

B.5.4. PRAC assessed procedures

PRAC Led
Bemfola - follitropin alfa -
EMA/H/C/002615/II/0016

Gedeon Richter Plc., Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Menno van der Elst, PRAC-CHMP liaison: Johann Lodewijk Hillege, "Update of the RMP version 2 based on the phase-3 multicentre study conducted to compare the efficacy and safety of two r-hFSH formulations in normal ovulatory women 35 to 42 years of age undergoing in vitro fertilisation (IVF) (CSR FIN3002)."

Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

PRAC Led
Bronchitol - mannitol -
EMA/H/C/001252/II/0031, Orphan

Pharmaxis Pharmaceuticals Limited,
Rapporteur: Nithyanandan Nagercoil, PRAC
Rapporteur: Julie Williams, PRAC-CHMP liaison:

Request for supplementary information adopted with a specific timetable.

Robert James Hemmings, "Submission of the final report of a survey of healthcare professionals listed as a category 3 study in the RMP. This is a final survey aimed to measure to the effectiveness of the educational materials at 6 months post-launch and 6 months post-redistribution of the revised healthcare professional leaflet. The RMP version 7.0 has also been submitted."
Request for Supplementary Information adopted on 12.04.2018.

PRAC Led
Edarbi - azilsartan medoxomil - EMEA/H/C/002293/II/0021
Takeda Pharma A/S, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Menno van der Elst, PRAC-CHMP liaison: Johann Lodewijk Hillege, "Submission of the final report from the drug utilisation study listed as a category 3 study in the RMP. This post-authorisation safety study is a retrospective non-interventional cohort study using a patient level electronic medical records database in Germany aimed to describe the prescription of azilsartan medoxomil in patients with essential hypertension and those prescribed azilsartan medoxomil for other reasons."
Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

PRAC Led
Eylea - aflibercept - EMEA/H/C/002392/II/0039
Bayer AG, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni, PRAC-CHMP liaison: Alexandre Moreau, "Submission of the final report from the post authorisation safety study 16526, listed as a category 3 study in the RMP. This is an observational study to evaluate the physician and patient knowledge of safety and safe use information for Aflibercept in Europe as stated in the EU Educational Material of Eylea."
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted on 08.02.2018, 30.11.2017.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led
Imraldi - adalimumab - EMEA/H/C/004279/II/0004
Samsung Bioepis UK Limited (SBUK),

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Ulla Wändel Liminga, PRAC-CHMP liaison: Kristina Dunder, "Submission of an updated RMP version 2.1 in order to indicate changes in the distribution method for the Imraldi Patient Alert Card (PAC) from being included in the Annex IIIA of the Product Information to be provided to patients by healthcare professionals by including the PAC in the physician educational material. The Annexes I, II, IIIA and IIIB of the PI are updated accordingly."
Opinion adopted on 12.04.2018.

PRAC Led

Lucentis - ranibizumab -

EMA/H/C/000715/II/0070/G

Novartis Europharm Limited, Rapporteur: Kristina Dunder, PRAC Rapporteur: Ulla Wändel Liminga, PRAC-CHMP liaison: Kristina Dunder, "1. Type II- C.I.13: Submission of the final report from study LUMINOUS study (CRFB002A2406), an observational, multicenter study to assess the long term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of the post-authorisation measures MEA 036, MEA 048 and MEA 054. Consequentially, the RMP has been updated to reflect these changes.

2. Type II-C.I.11: Submission of an updated RMP version 17.0 (RMP template Rev. 2) according to GVP Module V to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the use of educational materials and targeted follow-up checklists listed in Annex II-D of the Product Information."

Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

PRAC Led

MabThera - rituximab -

EMA/H/C/000165/II/0144

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Doris Stenver, PRAC-CHMP liaison: Sinan B. Sarac, "Update the RMP to remove the additional risk minimization measure of Educational Outreaches for the important identified risk of Infusion Related Reactions and Acute Infusion Related Reactions (IRR). Therefore, the RMP has been updated accordingly to version 16.0."

Request for Supplementary Information adopted

Request for supplementary information adopted with a specific timetable.

on 12.04.2018.

PRAC Led

**MULTAQ - dronedarone -
EMA/H/C/001043/II/0039/G**

sanofi-aventis groupe, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Menno van der Elst, PRAC-CHMP liaison: Johann Lodewijk Hillege, "C.I.13: Submission of the final report from study DRONE_C_05917 listed as a category 3 study in the RMP. This is a non-interventional epidemiological study aimed for the surveillance of serious liver injuries/diseases (SLD) with the use of dronedarone using multiple databases in the US, including the addendum on surveillance of interstitial lung disease (ILD). The RMP version 11.0 has also been submitted.

C.I.13: Submission of the final report from study DRONE_C_05911 listed as a category 3 study in the RMP. This is a non-interventional epidemiological study aimed to study the concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy). The RMP version 11.0 has also been submitted."

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 11.01.2018, 26.10.2017.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led

**Mycamine - micafungin -
EMA/H/C/000734/II/0035**

Astellas Pharma Europe B.V., Rapporteur: Harald Enzmann, PRAC Rapporteur: Martin Huber, PRAC-CHMP liaison: Harald Enzmann, "Submission of the final survey report regarding Educational tools in the RMP and Educational tools as a LEG (39) and updated RMP version 18.0."

Request for Supplementary Information adopted on 12.04.2018, 11.01.2018.

Request for supplementary information adopted with a specific timetable.

PRAC Led

**Nulojix - belatacept -
EMA/H/C/002098/II/0047/G**

Bristol-Myers Squibb Pharma EEIG, Rapporteur: Filip Josephson, PRAC Rapporteur: Ulla Wändel Liminga, PRAC-CHMP liaison: Filip Josephson, "Submission of the final report from studies IM103061 and IM103089, listed as a category 3

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

studies in the RMP.

IM103061 is an epidemiological study on pregnancy outcome among belatacept users in the US.

IM103089 evaluates data retrospectively to assess the association between belatacept and the risk of PTDL in renal transplant recipients in Europe.

An updated RMP, reflecting completion of the two above studies is being submitted as part of this variation (Version 15)."

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 30.11.2017.

PRAC Led

**NutropinAq - somatropin -
EMA/H/C/000315/II/0069/G**

Ipsen Pharma, PRAC Rapporteur: Doris Stenver, PRAC-CHMP liaison: Sinan B. Sarac, "II: C.I.11: Submission of an updated RMP version 3.0 in order to include formatting in accordance with the new RMP template and to include updates from the post-approval safety study (PASS) International Cooperative Growth Study (INCGS) Post Marketing Surveillance Program For NutropinAq.

II: C.I.13: Submission of the final report from International Cooperative Growth Study (INCGS) Post Marketing Surveillance Program For NutropinAq. This study collected long-term safety and effectiveness data on NutropinAq during treatment of paediatric growth disorders for which growth hormone is indicated."

Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led

**Pergoveris - follitropin alfa / lutropin alfa -
EMA/H/C/000714/II/0055**

Merck Serono Europe Limited, Rapporteur: Nithyanandan Nagercoil, PRAC Rapporteur: Julie Williams, PRAC-CHMP liaison: Greg Markey, "The update Risk Management Plan version 5.1 for Pergoveris to

- Align the RMP template with Good Pharmacovigilance Practice (GVP) Module V, revision 1.

- Add the reference to Pergoveris solution for injection in pre-filled pen (300IU/150IU, 450IU/225IU and 900IU/450IU) following the

Request for supplementary information adopted with a specific timetable.

approval in the European Union (EU) on the 8th of May 2017.

- Revise the epidemiology section based on the recent literature data.
- Revise non-clinical part of the safety specification section with the data available from r-hFSH (recombinant human follicle stimulating hormone), r-hLH (recombinant human luteinizing hormone) and Pergoveris. The clinical trial section has been updated for clinical studies for r-hFSH/r-hLH for Ovulation Induction (OI) and Assisted Reproductive Technologies (ART).
- Update the patient exposure data and other sections based on the cases received up to the data lock point (DLP) of 31 July 2017 i.e. non-study post authorisation exposure section and additional EU requirements for the safety specification section and include other minor changes such as update of the reporting rates.” Request for Supplementary Information adopted on 12.04.2018.

PRAC Led

**Resolor - prucalopride -
EMA/H/C/001012/II/0042**

Shire Pharmaceuticals Ireland Limited,
Rapporteur: Greg Markey, PRAC Rapporteur:
Patrick Batty, PRAC-CHMP liaison: Greg Markey,
“Submission of the final clinical study report for the post-authorization drug utilization study SHP555-804 in fulfilment of MEA 006.11 A drug utilisation study to examine characteristics of patients prescribed prucalopride (Resolor) and a pharmacoepidemiological study of the occurrence of major cardiovascular events, pregnancy, and pregnancy outcomes in the UK CPRD Database. The RMP (v 14.0) has also been updated to reflect the study results.”
Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

PRAC Led

**Tasigna - nilotinib -
EMA/H/C/000798/II/0092, Orphan**

Novartis Europharm Limited, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Doris Stenver, PRAC-CHMP liaison: Sinan B. Sarac,
“Submission of an updated RMP version 21.0 in order to delete the important identified risk 'Myelosuppression', and to upgrade the risk 'Cardiac failure' from an important potential to

Request for supplementary information adopted with a specific timetable.

an important identified risk. In addition, changes in the definition of the identified risks 'Hepatotoxicity' and 'Fluid retention' have been implemented.”
Request for Supplementary Information adopted on 12.04.2018.

PRAC Led
Xeljanz - tofacitinib -
EMA/H/C/004214/II/0009
Pfizer Limited, Rapporteur: Robert James Hemmings, PRAC Rapporteur: Sabine Straus, PRAC-CHMP liaison: Johann Lodewijk Hillege, “Submission of the final CSR for study A3921024 listed as a category 3 study in the RMP (MEA 003). Study A3921024 is a long term, open label follow-up study to evaluate the long-term safety of patients on 5 mg BID of XELJANZ with a secondary objective of evaluating sustained efficacy in patients with rheumatoid arthritis.”
Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led
Xofigo - radium-223 -
EMA/H/C/002653/II/0031
Bayer AG, Rapporteur: Harald Enzmann, PRAC Rapporteur: Patrick Batty, PRAC-CHMP liaison: Greg Markey, “Submission of Clinical Study Report for study 17399. This is an observational post-authorisation safety study (PASS) listed as category 4 in the RMP to evaluate the use of radium-223 dichloride in patients in Sweden with a diagnosis of CRPC with bone metastases (mCRPC) and patients in whom radium-223 dichloride may have been potentially used off-label.”
Opinion adopted on 12.04.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led
Zavicefta - ceftazidime / avibactam -
EMA/H/C/004027/II/0008
Pfizer Ireland Pharmaceuticals, PRAC Rapporteur: Jolanta Gulbinovic, PRAC-CHMP liaison: Rugile Pilviniene, “To provide an updated Risk Management Risk (version 2.0) in order to incorporate data from the REPROVE study (already submitted in procedure II-02), align the RMP with the current EU template, and add current post-marketing experience relative to the RMP data lock point (24/8/17). The Phase 3 REPROVE study was a randomized,

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

multicentre, double-blind, double-dummy, parallel group comparative study to determine the efficacy, safety and tolerability of CAZ-AVI (2000 mg ceftazidime and 500 mg avibactam) versus meropenem (1000 mg) in the treatment of NP, including VAP, in hospitalised adults 18 years of age or older.”

Opinion adopted on 12.04.2018.

PRAC Led

WS1283

Relvar Ellipta-

EMA/H/C/002673/WS1283/0035

Revinty Ellipta-

EMA/H/C/002745/WS1283/0031

Glaxo Group Ltd, Lead Rapporteur: Concepcion Prieto Yerro, Lead PRAC Rapporteur: Dolores Montero Corominas, PRAC-CHMP liaison: Concepcion Prieto Yerro, “Submission of a final study report 205052 (PRJ2214) (drug utilization study of new users of fluticasone furoate/vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study). The RMP version 9.1 has been updated accordingly.”

Opinion adopted on 12.04.2018.

Request for Supplementary Information adopted on 08.03.2018, 11.01.2018.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

PRAC Led

WS1299

Enurev Breezhaler-

EMA/H/C/002691/WS1299/0025

Seebri Breezhaler-

EMA/H/C/002430/WS1299/0025

Tovanor Breezhaler-

EMA/H/C/002690/WS1299/0028

Novartis Europharm Limited, Lead Rapporteur: Mark Ainsworth, Lead PRAC Rapporteur: Doris Stenver, PRAC-CHMP liaison: Sinan B. Sarac, “Submission of the final study report of the Category 1 Post-Authorisation Safety Study (PASS) on cardio and cerebrovascular outcomes (Multinational, multidatabase cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe / CNVA237A2402T) with subsequent update of Annex II. Consequently the deletion from the list of additional monitoring led to the update of Annex I and IIIB. The MAH also took this opportunity to update the local representatives.

Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

The RMP version 8 was submitted.”
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted
on 08.02.2018.

PRAC Led
WS1340
Ultibro Breezhaler-
EMA/H/C/002679/WS1340/0022
Ulunar Breezhaler-
EMA/H/C/003875/WS1340/0022
Xoterna Breezhaler-
EMA/H/C/003755/WS1340/0025

Novartis Europharm Limited, Lead Rapporteur:
Mark Ainsworth, Lead PRAC Rapporteur: Doris
Stenver, PRAC-CHMP liaison: Sinan B. Sarac,
“Submission of the final report of the
multinational, multi-database drug utilization
study of indacaterol/glycopyrronium bromide
(QVA149) in Europe (CQVA149A2401) with the
objective to estimate the use of QVA149 off-
label and in the subpopulations with missing
information mentioned in the risk management
plan (RMP).”

Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted
on 08.02.2018.

Positive Opinion adopted by consensus on
12.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

PRAC Led
WS1342
Exviera-EMA/H/C/003837/WS1342/0034
Viekirax-
EMA/H/C/003839/WS1342/0041

AbbVie Limited, Lead PRAC Rapporteur: Dolores
Montero Corominas, PRAC-CHMP liaison:
Concepcion Prieto Yerro, “To update the RMP to
incorporate changes requested by PRAC during
assessment of the 24 month PSUR applications
(EMA/H/C/PSUSA/00010363/201701 and
EMA/H/C/PSUSA/00010367/201701).

These changes are as follows:

1. Addition of a new potential risk of depression
and suicide in Module SVII.1 - Newly identified
safety concerns.
2. Removal of off-label use and medication error
as potential risks from Module SVII.
3. Renaming of the potential risk of
development of resistance to Lack of
Efficacy/Risk of Development of Resistance in
Module SVII.3.

In addition, the commitment dates for 4

Positive Opinion adopted by consensus on
12.04.2018. The Icelandic and Norwegian CHMP
Members were in agreement with the CHMP
recommendation.

ongoing studies listed in Part III.5.1 (Table of On-going and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan) have been revised.”
Opinion adopted on 12.04.2018.
Request for Supplementary Information adopted on 11.01.2018.

PRAC Led

WS1357

Efficib-EMEA/H/C/000896/WS1357/0089

Janumet-

EMEA/H/C/000861/WS1357/0089

Januvia-

EMEA/H/C/000722/WS1357/0063

Ristaben-

EMEA/H/C/001234/WS1357/0055

Ristfor-EMEA/H/C/001235/WS1357/0076

TESAVEL-

EMEA/H/C/000910/WS1357/0063

Velmetia-

EMEA/H/C/000862/WS1357/0092

Xelevia-EMEA/H/C/000762/WS1357/0067

Merck Sharp & Dohme Limited, Lead
Rapporteur: Johann Lodewijk Hillege, Lead
PRAC Rapporteur: Menno van der Elst, PRAC-
CHMP liaison: Johann Lodewijk Hillege,
“Submission of an updated RMP version 10 in order to remove “theoretic carcinogenic potential” form the list of safety concerns, currently classified as “missing information”.
Request for Supplementary Information adopted on 12.04.2018.

Request for supplementary information adopted with a specific timetable.

B.5.5. CHMP-CAT assessed procedures

Spherox - spheroids of human autologous matrix-associated chondrocytes -

EMEA/H/C/002736/II/0001, ATMP

CO.DON AG, Rapporteur: Lisbeth Barkholt,

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Spherox - spheroids of human autologous matrix-associated chondrocytes -

EMEA/H/C/002736/II/0002/G, ATMP

CO.DON AG, Rapporteur: Lisbeth Barkholt, ,
“Update of sections 4.2, 4.7, 4.8 and 5.1, of the SmPC in order to revise the wording and to update the safety and efficacy information based on the interim results from studies 16 HS 13 (24-month follow-up data) and 16 HS 14

Request for supplementary information adopted with a specific timetable.

(48-month follow-up data); the Package leaflet is updated accordingly.

Study 16 HS 13 is listed as a specific obligation post-authorisation efficacy study (PAES) in Annex II. It is a phase III, randomised, open label study aimed to evaluate the long-term efficacy and safety of Spherox vs. microfracture in patients with cartilage defects of the knee with a defect size between 1 and 4 cm².

Study 16 HS 14 is listed as a category 3 study in the RMP. It is a phase II, randomised, open label study, aimed to evaluate the efficacy and safety of the treatment of large defects (4-10 cm²) with 3 different doses of Spherox (ACT3D-CS) in subjects with cartilage defects of the knee."

Request for Supplementary Information adopted on 20.04.2018.

Zalmoxis - allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - EMEA/H/C/002801/II/0009/G, Orphan, ATMP

MolMed SpA, Rapporteur: Johannes Hendrikus Ovelgonne, CHMP Coordinator: Paula Boudewina van Hennik

Request for Supplementary Information adopted on 20.04.2018.

Request for supplementary information adopted with a specific timetable.

B.5.6. CHMP-PRAC-CAT assessed procedures

B.5.7. PRAC assessed ATMP procedures

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

WS1341/G

Tivicay-

EMEA/H/C/002753/WS1341/0033/G

Triumeq-

EMEA/H/C/002754/WS1341/0052/G

ViiV Healthcare UK Limited, Lead Rapporteur:

Filip Josephson

Opinion adopted on 19.04.2018.

Positive Opinion adopted by consensus.

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

<p>WS1345/G Ebymect- EMA/H/C/004162/WS1345/0030/G Edistride- EMA/H/C/004161/WS1345/0024/G Forxiga- EMA/H/C/002322/WS1345/0043/G Qtern- EMA/H/C/004057/WS1345/0015/G Xigduo- EMA/H/C/002672/WS1345/0041/G AstraZeneca AB, Lead Rapporteur: Kristina Dunder Opinion adopted on 19.04.2018.</p>	<p>Positive Opinion adopted by consensus. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>WS1350 Hexacima- EMA/H/C/002702/WS1350/0078 Hexaxim- EMA/H/W/002495/WS1350/0083 Hexyon- EMA/H/C/002796/WS1350/0082 Sanofi Pasteur Europe, Duplicate, Duplicate of Hexacima, Lead Rapporteur: Jan Mueller-Berghaus, Request for Supplementary Information adopted on 26.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>WS1358 AMGEVITA- EMA/H/C/004212/WS1358/0004 SOLYMBIC- EMA/H/C/004373/WS1358/0004 Amgen Europe B.V., Lead Rapporteur: Kristina Dunder, Opinion adopted on 12.04.2018.</p>	<p>Positive Opinion adopted by consensus on 12.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>
<p>WS1361 AZILECT- EMA/H/C/000574/WS1361/0079 Rasagiline ratiopharm- EMA/H/C/003957/WS1361/0012 Teva B.V., Lead Rapporteur: Bruno Sepodes, Request for Supplementary Information adopted on 12.04.2018.</p>	<p>Request for supplementary information adopted with a specific timetable.</p>
<p>WS1367 Abseamed- EMA/H/C/000727/WS1367/0069 Binocrit- EMA/H/C/000725/WS1367/0069 Epoetin alfa Hexal- EMA/H/C/000726/WS1367/0068 Sandoz GmbH, Lead Rapporteur: Alexandre</p>	<p>Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.</p>

Moreau,
Opinion adopted on 19.04.2018.

WS1373/G
AMGEVITA-
EMA/H/C/004212/WS1373/0005/G
SOLYMBIC-

EMA/H/C/004373/WS1373/0005/G

Amgen Europe B.V., Lead Rapporteur: Kristina Dunder, "To update SmPC section 5.1 with the clinical interim data from OLE study M11-327. To update section 2 of the Package Leaflet to include a clarifying statement that allergic reactions to the product can in rare cases be life-threatening.

In addition the MAH updated the PL and LT annexes to be in line with the originators annexes."

Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

WS1375
Actraphane-
EMA/H/C/000427/WS1375/0075
Insulatard-

EMA/H/C/000441/WS1375/0072

Mixtard-

EMA/H/C/000428/WS1375/0076

Protaphane-

EMA/H/C/000442/WS1375/0071

Novo Nordisk A/S, Duplicate, Duplicate of Monotard (SRD), Ultratard (SRD), Lead Rapporteur: Sinan B. Sarac "To update section 4.2 of the SmPC in order to implement the PRAC signal recommendations on 'Insulin (pre-filled pens and cartridges) for potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia' (EPITT no. 18893) adopted at the 30 November 2017 PRAC meeting. Sections 2 and 3 of the PL have been updated accordingly. As a consequence passive discouragement recommended by the PRAC was included in section 4.2 of the SmPC and sections 2 and 3 of the PL. In addition, the MAH took the opportunity to revise the manufacturer batch code for Site Chartres, France in section 6 of the PLs of the vial."

Opinion adopted on 26.04.2018.

Positive Opinion adopted by consensus on 26.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation.

Hexacima-
EMA/H/C/002702/WS1304/0076
Hexaxim-

Positive Opinion adopted by consensus on 19.04.2018. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP

EMEA/H/W/002495/WS1304/0081 recommendation.

Hexyon-

EMEA/H/C/002796/WS1304/0080

Sanofi Pasteur, Lead Rapporteur: Jan Mueller-Berghaus,

Opinion adopted on 19.04.2018.

Request for Supplementary Information adopted on 15.02.2018.

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

Jinarc - tolvaptan -

EMEA/H/C/002788/II/0013

Otsuka Pharmaceutical Europe Ltd, Rapporteur: Greg Markey

Withdrawal request submitted on 29.03.2018.

The MAH withdrew the procedure on 29.03.2018.

Pyramax - pyronaridine / artesunate -

EMEA/H/W/002319/II/0018

Shin Poong Pharmaceutical Co., Ltd.,

Rapporteur: Joseph Emmerich, PRAC

Rapporteur: Caroline Laborde

Withdrawal request submitted on 06.04.2018.

The MAH withdrew the procedure on 06.04.2018.

Qtern - saxagliptin / dapagliflozin -

EMEA/H/C/004057/II/0013

AstraZeneca AB, Rapporteur: Johann Lodewijk

Hillege, Withdrawal request submitted on

03.04.2018.

The MAH withdrew the procedure on 03.04.2018.

Resolor - prucalopride -

EMEA/H/C/001012/II/0044

Shire Pharmaceuticals Ireland Limited,

Rapporteur: Greg Markey

Withdrawal request submitted on 26.03.2018.

The MAH withdrew the procedure on 26.03.2018.

Samsca - tolvaptan -

EMEA/H/C/000980/II/0029

Otsuka Pharmaceutical Europe Ltd, Rapporteur:

Greg Markey

Withdrawal request submitted on 29.03.2018.

The MAH withdrew the procedure on 29.03.2018.

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

Imbruvica - ibrutinib -

EMEA/H/C/003791/II/0029, Orphan

MAH: Janssen-Cilag International NV,

Rapporteur: Filip Josephson, PRAC Rapporteur:

Julie Williams "Update of sections 4.5 of the

SmPC to remove the statement that an

interaction between products increasing

stomach pH and ibrutinib have not been studied

Request for clock stop extension.

Adopted.

and section 5.2 to include the findings from study CLL1005. The Package Leaflet is not impacted by these changes.

In addition, the RMP is updated to version 6.3 to reflect this new safety information.”

RSI adopted 15.12.2016

Cimzia - certolizumab pegol - EMEA/H/C/001037/II/0068/G	Request for clock stop extension.
UCB Pharma S.A., Rapporteur: Kristina Dunder	Adopted.
Request for Supplementary Information adopted on 15.03.2018.	

B.6. START OF THE PROCEDURES TIMETABLES FOR INFORMATION

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

atazanavir - EMEA/H/C/004859

, treatment of HIV-1 infection

turoctocog alfa pegol - EMEA/H/C/004883, Orphan

Novo Nordisk A/S, Treatment and prophylaxis of bleeding in patients with haemophilia A

cemiplimab - EMEA/H/C/004844

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

ciprofloxacin - EMEA/H/C/004394

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

miglustat - EMEA/H/C/004904

, treatment of adult patients with mild to moderate type 1 Gaucher disease and only in the treatment of patients for whom enzyme replacement therapy is unsuitable,

pegvaliase - EMEA/H/C/004744, Orphan

BioMarin International Limited, treatment of adults with phenylketonuria (PKU) who have inadequate blood phenylalanine control

axalimogene filolisbac - EMEA/H/C/004473, ATMP

, treatment of cervical cancer

Ianadelumab - EMEA/H/C/004806, Orphan Accelerated review

Shire Pharmaceuticals Ireland Limited,

prevention of angioedema attacks, treatment of angioedema attacks

sotagliflozin - EMEA/H/C/004889, indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus.

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

Dupixent - dupilumab - EMEA/H/C/004390/X/0004/G

sanofi-aventis groupe, Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Peter Kiely, PRAC Rapporteur: Kimmo Jaakkola, "Extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP), grouped with a type II variation (C.I.6.a) to add the following indications:

- Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype;
- Maintenance therapy to improve lung function;
- Maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients;

Based on the pivotal studies DRI12544, QUEST and VENTURE.

As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated accordingly.

The RMP (version 2.0) is updated accordingly. In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths."

Orencia - abatacept - EMEA/H/C/000701/X/0117/G

Bristol-Myers Squibb Pharma EEIG, Rapporteur: Outi Mäki-Ikola, PRAC Rapporteur: Kirsti Villikka, "Extension application to add 2 new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard, for subcutaneous (SC) administration, grouped with a type II variation (C.I.6.a) to include paediatric use of polyarticular Juvenile

Idiopathic Arthritis (2 years and above) for solution for injection (50 mg, 87.5 mg and 125 mg).

The above-described changes are grouped with variations:

The RMP (version 25.0) is updated in accordance.

In addition, the applicant took the opportunity to implement minor editorial changes in the product information.”

**Xeljanz - tofacitinib -
EMA/H/C/004214/X/0012**

Pfizer Limited, Rapporteur: Robert James Hemmings, PRAC Rapporteur: Sabine Straus, “Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90, and 91 tablets.

The extension of indication includes a change in pharmacokinetics.

An updated RMP (version 4.0) has been provided.”

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

viable t-cells - EMA/H/C/002397, Orphan, ATMP

Kiadis Pharma Netherlands B.V., adjunctive treatment in haematopoietic stem cell transplantation (HSCT) for a malignant disease
List of Questions adopted on 08.09.2017.

glycopyrronium / formoterol fumarate dihydrate - EMA/H/C/004245

, indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

List of Questions adopted on 09.11.2017.

encorafenib - EMA/H/C/004580

, in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation

List of Questions adopted on 14.12.2017.

deferiprone - EMA/H/C/004710

, treatment of iron overload in thalassemia major,

List of Questions adopted on 09.11.2017.

gefitinib - EMEA/H/C/004826

, treatment of non-small cell lung cancer,
List of Questions adopted on 14.12.2017.

durvalumab - EMEA/H/C/004771

, treatment of locally advanced, unresectable
non-small cell lung cancer (NSCLC)
List of Questions adopted on 25.01.2018.

**Inhixa - enoxaparin sodium -
EMEA/H/C/004264/X/0018**

Techdow Europe AB, Duplicate, Duplicate of
Thorinane, Rapporteur: Andrea Laslop, PRAC
Rapporteur: Menno van der Elst, "Extension
application to add two new strengths of 12,000
IU (120 mg)/0.8 mL and 15,000 IU (150 mg)/1
mL for enoxaparin sodium solution for injection
in pre-filled syringe, for subcutaneous,
extracorporeal and intravenous administration."
List of Questions adopted on 14.12.2017.

**tisagenlecleucel - EMEA/H/C/004090,
Orphan, ATMP**

Novartis Europharm Limited, treatment of B cell
acute lymphoblastic leukaemia (ALL) and diffuse
large B cell lymphoma (DLBCL), CHMP
Coordinators: Bjorg Bolstad, Greg Markey
List of Questions adopted on 16.03.2018.

lenalidomide - EMEA/H/C/004857

, treatment of multiple myeloma, Generic,
Generic of Revlimid
List of Questions adopted on 14.12.2017.

**voretigene neparvovec -
EMEA/H/C/004451, Orphan, ATMP**

Spark Therapeutics Ireland Ltd, treatment of
patients with vision loss due to Leber congenital
amaurosis or retinitis pigmentosa inherited
retinal dystrophy
List of Questions adopted on 08.12.2017.

binimetinib - EMEA/H/C/004579

, in combination with encorafenib is indicated for
the treatment of adult patients with
unresectable or metastatic melanoma with a
BRAF V600 mutation
List of Questions adopted on 14.12.2017.

melatonin - EMEA/H/C/004425, PUMA

, treatment of insomnia in children with Autism
Spectrum Disorders and neurogenetic diseases

List of Questions adopted on 14.09.2017.

mexiletine hcl - EMEA/H/C/004584, Orphan

LUPIN (EUROPE) LIMITED, Treatment of myotonic disorders

List of Questions adopted on 14.12.2017.

paclitaxel - EMEA/H/C/004441

, treatment of metastatic breast cancer, Generic, Generic of Abraxane

List of Questions adopted on 14.12.2017.

pegfilgrastim - EMEA/H/C/003961

, treatment of neutropenia

List of Questions adopted on 14.09.2017.

inotersen - EMEA/H/C/004782, Orphan

IONIS USA Ltd, treatment of transthyretin amyloidosis (hATTR)

List of Outstanding Issues adopted on 24.04.2018.

List of Questions adopted on 20.02.2018.

meropenem / vaborbactam - EMEA/H/C/004669

, treatment of urinary tract infection (cUTI), including pyelonephritis, intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), bacteraemia, infections due to bacterial organisms

List of Questions adopted on 09.11.2017.

daunorubicin / cytarabine - EMEA/H/C/004282, Orphan

Jazz Pharmaceuticals Ireland Limited, treatment of adults with high-risk acute myeloid leukaemia (AML)

List of Outstanding Issues adopted on 24.04.2018.

List of Questions adopted on 20.02.2018.

eravacycline - EMEA/H/C/004237

, treatment of complicated intra-abdominal infections (cIAI) in adults

List of Questions adopted on 14.12.2017.

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

Firdapse - amifampridine -

EMEA/H/C/001032/S/0053, Orphan

BioMarin Europe Ltd, Rapporteur: Greg Markey,

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

Bavencio - avelumab -

EMA/H/C/004338/R/0003, Orphan

Merck Serono Europe Limited, Rapporteur: Filip

Josephson, PRAC Rapporteur: Doris Stenver

Fluenz Tetra - influenza vaccine (live attenuated, nasal) -

EMA/H/C/002617/R/0079

AstraZeneca AB, Rapporteur: Bart Van der

Schueren, Co-Rapporteur: Svein Rune

Andersen, PRAC Rapporteur: Jean-Michel Dogné

Memantine Accord - memantine -

EMA/H/C/002766/R/0010

Accord Healthcare Limited, Generic, Generic of

Axura, Rapporteur: Milena Stain, PRAC

Rapporteur: Dolores Montero Corominas

B.6.6. VARIATIONS – START OF THE PROCEDURE

Timetables for adoption provided that the validation has been completed.

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

CABOMETYX - cabozantinib -

EMA/H/C/004163/II/0005

Ipsen Pharma, Rapporteur: Robert James

Hemmings, Co-Rapporteur: Bjorg Bolstad, PRAC

Rapporteur: Sabine Straus, "Extension of

indication to include the treatment of advanced

hepatocellular carcinoma in adults following

prior systemic therapy for Cabometyx; as a

consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1,

5.2 of the SmPC are updated with safety and

efficacy information. The package leaflet and

the risk management plan (version 4.0) are also

updated accordingly."

Kalydeco - ivacaftor -

EMA/H/C/002494/II/0069, Orphan

Vertex Pharmaceuticals (Europe) Ltd., Co-

Rapporteur: Melinda Sobor, PRAC Rapporteur:

Dolores Montero Corominas, "Extension of

Indication to include treatment of cystic fibrosis

in children age 12 to less than 24 months who

have one of the currently approved gating

mutations in the CFTR gene for Kalydeco 50 mg

& 75 mg Granules; as a consequence, sections

4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to the Kalydeco 150 mg film-coated tablet Product Information. The Package Leaflet is updated in accordance.
The RMP version 7.2 has also been submitted.”

**Keytruda - pembrolizumab -
EMA/H/C/003820/II/0043**

Merck Sharp & Dohme Limited, Rapporteur:
Daniela Melchiorri, Co-Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Sabine Straus,
“Extension of Indication to include 1st line treatment of non-squamous non-small cell lung cancer (NSCLC) in combination with pemetrexed and platinum chemotherapy based on the efficacy and safety data from pivotal study KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G.
KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab + pemetrexed + carboplatin or cisplatin (pembro combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance.
An updated RMP version 16.2 was provided as part of the application.”

**Lynparza - olaparib -
EMA/H/C/003726/II/0020**

AstraZeneca AB, Rapporteur: Alexandre Moreau, Co-Rapporteur: Bart Van der Schueren, PRAC Rapporteur: Carmela Macchiarulo, “Extension of indication to include the use of Lynparza tablets as a monotherapy for the treatment of adult patients with BRCA1/2-mutated HER2 negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.
As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Lynparza tablets have been updated. Section 4.8 of Lynparza capsules and relevant sections of the package leaflet have been updated accordingly.

Furthermore, RMP version 16 has also been provided.”

**MabThera - rituximab -
EMA/H/C/000165/II/0149**

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Doris Stenver, “Extension of indication to include the maintenance of remission of polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA) for MabThera; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II.”

**MabThera - rituximab -
EMA/H/C/000165/II/0150**

Roche Registration GmbH, Rapporteur: Sinan B. Sarac, Co-Rapporteur: Paula Boudewina van Hennik, PRAC Rapporteur: Doris Stenver, “Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV) for MabThera; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly.”

**Rapiscan - regadenoson -
EMA/H/C/001176/II/0027**

GE Healthcare AS, Rapporteur: Greg Markey, PRAC Rapporteur: Patrick Batty, “Extension of Indication to include use in the measurement of fractional flow reserve (FFR) during invasive coronary angiography (ICA) in patients presenting a coronary artery stenosis for Rapiscan based on study 060912001: Comparison of Regadenoson (RAPISCAN) and Central Intravenous Adenosine for Measurement of Fractional Flow Reserve and data from published literature. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP version 10.0 was provided as part of this extension of indication.”

**RoActemra - tocilizumab -
EMA/H/C/000955/II/0076**

Roche Registration GmbH, Rapporteur: Jan Mueller-Berghaus, Co-Rapporteur: Agnes Gyurasics, PRAC Rapporteur: Brigitte Keller-Stanislawski, “To add the paediatric indication ‘treatment of active systemic juvenile idiopathic

arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids' to the RoActemra 162 mg solution for injection in pre-filled syringe formulation, based on data from the Phase Ib pharmacokinetic/pharmacodynamic bridging study WA28118 (JIGSAW 118), designed to confirm the RoActemra subcutaneous dosing regimens in patients aged 1 to 17 years old with sJIA, as well as assess the safety of the RoActemra subcutaneous formulation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated accordingly. In addition, sections 4.2, 4.8 and 5.2 of the SmPC of the RoActemra 20 mg/mL concentrate for solution for infusion formulation are updated to reflect data from the pivotal RoActemra intravenous study WA18221 (TENDER), a randomised, placebo-controlled study to evaluate the effect of tocilizumab on disease response in patients with active sJIA."

**Trimbow - beclometasone dipropionate /
formoterol fumarate dihydrate /
glycopyrronium -
EMA/H/C/004257/II/0002**

Chiesi Farmaceutici S.p.A., Rapporteur: Harald Enzmann, PRAC Rapporteur: Jan Neuhauser, "Extension of Indication for Trimbow to all adult patients with moderate or severe chronic obstructive pulmonary disease (COPD).

as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated in order to add the results of two Phase III studies (Triple 7 and Triple 8);

Triple 7 (CCD-05993AA1-07) is a multinational, multicentre, randomised, open-label, active-controlled, 26-week, 2-arm, parallel group study to evaluate the non-inferiority of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pressurised metered dose inhaler (pMDI) (CHF 5993) versus (vs.) fixed combination of fluticasone furoate plus vilanterol administered via dry powder inhaler (DPI) (Relvar®) plus tiotropium bromide (Spiriva®) for the treatment of patients with Chronic Obstructive Pulmonary

Disease (COPD).

Triple 8 (CCD-05993AA1-08) is a 52-week, double blind, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro®) via DPI in patients with Chronic Obstructive Pulmonary Disease (TRIBUTE)

The Package Leaflet and the Risk Management Plan are updated in accordance."

B.6.8. CHMP assessed procedures scope: Pharmaceutical aspects

Adjupanrix - pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) -

EMA/H/C/001206/II/0058/G

GlaxoSmithKline Biologicals SA, Informed Consent of Pandemrix (EXP), Rapporteur: Greg Markey

Armisarte - pemetrexed -

EMA/H/C/004109/II/0017/G

Actavis Group PTC ehf, Rapporteur: Alar Irs

BiResp Spiromax - budesonide / formoterol

- EMA/H/C/003890/II/0024/G

Teva Pharma B.V., Duplicate, Duplicate of DuoResp Spiromax, Rapporteur: Nithyanandan Nagercoil

DuoResp Spiromax - budesonide / formoterol -

EMA/H/C/002348/II/0024/G

Teva Pharma B.V., Rapporteur: Nithyanandan Nagercoil

Elaprase - idursulfase -

EMA/H/C/000700/II/0077/G

Shire Human Genetic Therapies AB, Rapporteur: Greg Markey

Eptifibatide Accord - eptifibatide -

EMA/H/C/004104/II/0004

Accord Healthcare Limited, Generic, Generic of Integrilin, Rapporteur: Jayne Crowe

Eylea - aflibercept -

EMA/H/C/002392/II/0046

Bayer AG, Rapporteur: Alexandre Moreau

Inhixa - enoxaparin sodium -

EMA/H/C/004264/II/0031

Techdow Europe AB, Duplicate, Duplicate of
Thorinane, Rapporteur: Andrea Laslop

Insuman - insulin human -

EMA/H/C/000201/II/0124

Sanofi-Aventis Deutschland GmbH, Rapporteur:
Bart Van der Schueren

Kevzara - sarilumab -

EMA/H/C/004254/II/0006/G

sanofi-aventis groupe, Rapporteur: Jan Mueller-
Berghaus

Keytruda - pembrolizumab -

EMA/H/C/003820/II/0046

Merck Sharp & Dohme Limited, Rapporteur:
Daniela Melchiorri

Lemtrada - alemtuzumab -

EMA/H/C/003718/II/0021/G

Genzyme Therapeutics Ltd, Duplicate, Duplicate
of Lemtrada (WD), Rapporteur: Mark Ainsworth

MabThera - rituximab -

EMA/H/C/000165/II/0151

Roche Registration GmbH, Rapporteur: Sinan B.
Sarac

Prepandrix - A/Indonesia/05/2005

(H5N1) like strain used (PR8-IBCDC-RG2) -

EMA/H/C/000822/II/0075/G

GlaxoSmithkline Biologicals SA, Rapporteur:
Greg Markey

Simponi - golimumab -

EMA/H/C/000992/II/0082/G

Janssen Biologics B.V., Rapporteur: Kristina
Dunder

**Synflorix - pneumococcal polysaccharide
conjugate vaccine (adsorbed) -**

EMA/H/C/000973/II/0125

GlaxoSmithkline Biologicals SA, Rapporteur:
Kristina Dunder

**Vaxelis - diphtheria, tetanus, pertussis
(acellular, component), hepatitis B (rDNA),
poliomyelitis (inact.) and Haemophilus
type B conjugate vaccine (adsorbed) -**

EMA/H/C/003982/II/0030

MCM Vaccine B.V., Rapporteur: Bart Van der

Schueren

WS1376/G

Blitzima-

EMA/H/C/004723/WS1376/0013/G

Ritemvia-

EMA/H/C/004725/WS1376/0013/G

Rituzena-

EMA/H/C/004724/WS1376/0014/G

Truxima-

EMA/H/C/004112/WS1376/0014/G

Celltrion Healthcare Hungary Kft., Lead

Rapporteur: Sol Ruiz

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

Afinitor - everolimus -

EMA/H/C/001038/II/0058

Novartis Europharm Limited, Rapporteur: Harald Enzmann, "Submission of the final report from study CRAD001Y2201, listed as a category 1 study in the RMP. This is a three arm randomised study investigating the combination of everolimus with exemestane versus everolimus alone versus capecitabine in patients with oestrogen receptor positive metastatic breast cancer after recurrence or progression on letrozole or anastrozole. Consequently, Annex II of the Product Information was updated to remove this study."

Ceprothin - human protein C -

EMA/H/C/000334/II/0104

Baxter AG, Rapporteur: Jan Mueller-Berghaus, "Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information of Ceprothin based on an update of the Company Core Safety Information.

The Package Leaflet has been further updated."

Cyramza - ramucirumab -

EMA/H/C/002829/II/0023/G

Eli Lilly Nederland B.V., Rapporteur: Paula Boudewina van Hennik, "Submission of the final report from study Study I4T-MC-JVCZ Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma and Study I4T-MC-JVDB Randomized Phase 2 Trial

Evaluating Pharmacokinetics and Safety of Four Ramucirumab Dosing Regimens in Second Line Gastric or Gastroesophageal Junction Adenocarcinoma in fulfilment with Annex II condition linked to Cyramza Marketing Authorisation. Annex II of the product information has been updated accordingly.”

Elaprase - idursulfase -

EMA/H/C/000700/II/0076

Shire Human Genetic Therapies AB, Rapporteur: Greg Markey, “Update of section 4.8 of the SmPC to update the frequency category of the following adverse drug reactions: hypertension, tachypnoea, dyspepsia, erythema and infusion-site swelling, based on a routine review and update of the idursulfase CCDS. The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to implement some minor corrections to the SmPC.”

Gardasil 9 - human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) -

EMA/H/C/003852/II/0024/G

MSD Vaccins, Rapporteur: Kristina Dunder, “Update of section 5.1 of the SmPC in order to update the information following results from long-term follow-up (LTFU) studies. Specifically:

- a long-term effectiveness sub-section is added, based on the first interim reports from the 9vHPV studies V503-021-01 and V503-002-20 (two category 3 studies included in the pharmacovigilance plan of the 9vHPV vaccine - MEA-004 and MEA 005, respectively).
 - update of the immunogenicity sub-section based on the data from the two 9vHPV studies listed above as well as final results from studies V503-001-04 and V503-010-01.
 - update of the qHPV clinical data based on the efficacy/effectiveness results and/or immunogenicity results of the qHPV studies V501-015-21 (4th interim report), V501-019-21 (final study report), V501-020-21 (final study report) and the extension of study V501-167.”
-

Humira - adalimumab -

EMA/H/C/000481/II/0179

AbbVie Deutschland GmbH & Co. KG, Rapporteur: Kristina Dunder, “Update of section

4.8 of the SmPC in order to add Lichenoid skin reactions with a rare frequency following a signal detection request (EPITT ref. No. 19128) for cumulative review (SDA106). The Package Leaflet is updated accordingly”

**HyQvia - human normal immunoglobulin -
EMA/H/C/002491/II/0040/G**

Baxalta Innovations GmbH, Rapporteur: Jan Mueller-Berghaus, “Update of section 4.8 of the SmPC to include aseptic meningitis as adverse reaction. The PL is updated accordingly.

Update of section 4.2 of the SmPC to include the option of handpush administration of the rHuPH20 component (in addition to administration with a pump). This change is a correction in order to harmonize with the PIL.”

Iclusig - ponatinib -

EMA/H/C/002695/II/0045/G, Orphan

Incyte Biosciences UK Ltd, Rapporteur: Greg Markey, “Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to reflect updated safety and efficacy information based on data from final study AP24534-10-201 (PACE) “ A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia” , as well as data from final study AP24534-07-101 “A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukemia and other Hematologic Malignancies”. The Package Leaflet is updated accordingly.”

Imbruvica - ibrutinib -

EMA/H/C/003791/II/0042, Orphan

Janssen-Cilag International NV, Rapporteur: Filip Josephson, “Update of section 5.3 of the SmPC in order to update preclinical safety data information based on final results from a non-clinical carcinogenicity study in mouse (MEA011.1). In addition, the Marketing authorisation holder (MAH) took the opportunity to align the Package leaflet to information already included in the SmPC and to update the list of local representatives for Lithuania, Czech Republic, Netherlands and Portugal in the Package Leaflet.”

Jinarc - tolvaptan -

EMA/H/C/002788/II/0015

Otsuka Pharmaceutical Europe Ltd, Rapporteur:
Greg Markey, "Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on acute liver failure requiring liver transplantation, based post-marketing experience with tolvaptan in autosomal dominant polycystic kidney disease (ADPKD).
The Package Leaflet is updated accordingly."

**Keytruda - pembrolizumab -
EMA/H/C/003820/II/0044**

Merck Sharp & Dohme Limited, Rapporteur:
Daniela Melchiorri, "Update of section 5.1 of the SmPC in order to reflect the final overall survival efficacy data from study Keynote-024; a randomized, open-label phase III trial of pembrolizumab versus platinum based chemotherapy in 1L subjects with PD-L1 strong metastatic non-small cell lung cancer (NSCLC)."

**Kuvan - sapropterin -
EMA/H/C/000943/II/0059, Orphan**

BioMarin International Limited, Rapporteur:
Peter Kiely, "As requested following the Art 46 procedure assessment, update of section 5.1 of the SmPC to reflect the data of the final clinical study report for the long term extension phase of the SPARK study. Sections 4.2 and 4.4 are also updated."

**Ozempic - semaglutide -
EMA/H/C/004174/II/0001**

Novo Nordisk A/S, Rapporteur: Johann Lodewijk Hillege, "Update of section 5.1 of the SmPC in order to reflect final results from the SUSTAIN 7 trial (NN9535-4216), a 40-week open-label trial comparing the safety and efficacy of 0.5 mg of Ozempic to 0.75 mg of dulaglutide and 1 mg of Ozempic to 1.5 mg of dulaglutide in patients on metformin with type-2 diabetes."

**Revestive - teduglutide -
EMA/H/C/002345/II/0043, Orphan**

Shire Pharmaceuticals Ireland Limited,
Rapporteur: Mark Ainsworth, "Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the final CSR of study TED-C14-006 ("a 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years With Short Bowel Syndrome who are Dependent on Parenteral

Support"; a category 3 study in the RMP). The Package Leaflet is updated accordingly."

Samsca - tolvaptan -

EMA/H/C/000980/II/0030

Otsuka Pharmaceutical Europe Ltd, Rapporteur: Greg Markey, "Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on acute liver failure requiring liver transplantation, based post-marketing experience with tolvaptan in autosomal dominant polycystic kidney disease (ADPKD). The Package Leaflet is updated accordingly."

Savene - dexrazoxane -

EMA/H/C/000682/II/0036

Clinigen Healthcare Ltd, Rapporteur: Alexandre Moreau, "Update of section 4.4 and 4.6 of the SmPC in order to add a warning on mutagenic activity of dexrazoxane and to update the contraception recommendations based on toxicological data and literature review, the Package Leaflet is updated accordingly. In addition the MAH took the opportunity to make an administrative amendment to the description of the pharmaceutical form for Savene in order to align with the relevant EDQM standard terms."

Taltz - ixekizumab -

EMA/H/C/003943/II/0018

Eli Lilly Nederland B.V., Rapporteur: Kristina Dunder, "Update of section 5.1 of the SmPC, providing a short summary of the results of study RHBO A Multicenter, Randomized, Double-Blind Study Comparing the Efficacy and Safety of Ixekizumab Versus Placebo in Patients with Moderate-to-Severe Genital Psoriasis."

Truvada - emtricitabine / tenofovir disoproxil - EMA/H/C/000594/II/0147

Gilead Sciences International Limited, Rapporteur: Greg Markey, "Update of sections 4.8 and 5.1 of the Truvada SmPC based on the final results from study Study ATN-113 (CO-US-164-0455): listed as a category 3 study in the RMPI; this is a Project PeEPare - An open label demonstration project and phase II safety study of pre-exposure prophylaxis use among 15 to 17 year old men who have sex with men (YMSM) in the United States."

WS1346**Aprovel-****EMEA/H/C/000141/WS1346/0170****CoAprovel-****EMEA/H/C/000222/WS1346/0185****Irbesartan Hydrochlorothiazide Zentiva-****EMEA/H/C/000783/WS1346/0099****Irbesartan Zentiva-****EMEA/H/C/000785/WS1346/0078****Karvea-EMEA/H/C/000142/WS1346/0174****Karvezide-****EMEA/H/C/000221/WS1346/0187**

Sanofi Clir SNC, Lead Rapporteur: Concepcion Prieto Yerro, "Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information for irbesartan and for irbesartan/ hydrochlorothiazide linked to irbesartan INN by adding "Psoriasis : the use of irbesartan in patients with psoriasis or a history of psoriasis should be carefully weighed as it may exacerbate psoriasis" and include new undesirable effects "anaphylactic reaction including anaphylactic shock", "psoriasis", "photosensitivity"; and update of the corresponding section of PL.

In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10."

WS1359**Invega-EMEA/H/C/000746/WS1359/0059****Trevicta-****EMEA/H/C/004066/WS1359/0012****Xeplion-EMEA/H/C/002105/WS1359/0038**

Janssen-Cilag International NV, Lead Rapporteur: Kristina Dunder, "Update of section 4.8 of the SmPC in order to include somnambulism and sleep-related eating disorder under a rare and not know frequency respectively after post marketing reports analysis. The Package Leaflet is updated accordingly.

In addition, for INVEGA/XEPLION/TREVICTA the details of the local representatives in Portugal, Belgium and Luxembourg are updated in the Package Leaflet.

An update is also proposed to the INVEGA Package Leaflet at section 2 to add a standard statement concerning sodium content according

to "Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use". Updated wording to align to the Excipients Guideline is also proposed for Risperdal Oral, together with removing the brand name (West Medimop) for the vial adaptors for Risperdal Consta."

WS1362

Enbrel-EMEA/H/C/000262/WS1362/0217

LIFMIOR-

EMEA/H/C/004167/WS1362/0014

Pfizer Limited, Lead Rapporteur: Robert James Hemmings, "Submission of the final report from the study 20050111 listed as category 3 study in the RMP, in order to fulfil Enbrel P46 0134.2. This is a multicentre, open-label extension study to evaluate the long-term safety and efficacy of etanercept in paediatric subjects with moderate to severe plaque psoriasis for up to 264 weeks (or until the quarterly visit after the subject's 18th birthday, whichever comes last) who participated in controlled study 20030211."

WS1371

Rasilez-EMEA/H/C/000780/WS1371/0119

Rasilez HCT-

EMEA/H/C/000964/WS1371/0086

Noden Pharma DAC, Lead Rapporteur: Daniela Melchiorri, "Update of section 4.8 and 5.1 of the Rasilez SmPC and section 4.8 of the Rasilez/HCTZ SmPC in order to reflect the results from paediatric study CSPP100A2365E2 (a multicenter, 52 to 104 week extension study to evaluate the long term growth and development of pediatric hypertensive patients 6–17 years of age treated previously with aliskiren) provided as per the requirement of article 46."

WS1381

Leganto-

EMEA/H/C/002380/WS1381/0027

Neupro-EMEA/H/C/000626/WS1381/0082

UCB Pharma S.A., Informed Consent of Neupro, Lead Rapporteur: Bruno Sepodes, "Update of section 4.8 of the SmPC in order to add an adverse drug reaction: Dropped Head Syndrome based on new pharmacovigilance data; The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA)

took the opportunity to correct some discrepancies found within the PIL of Greece, Cyprus and Romania and to update the Neupro Annex A in alignment with Leganto Annex A for the description of the multipack size.”

WS1391

Epclusa-

EMA/H/C/004210/WS1391/0026

Vosevi-EMA/H/C/004350/WS1391/0014

Gilead Sciences International Limited, Lead Rapporteur: Filip Josephson, “Update of section 5.3 of the SmPC based on data from a 2-year rat carcinogenicity study TX-281-2030. In addition, the MAH took the opportunity to update the ATC code in line with the new classification of antivirals for treatment of HCV infections and to introduce minor linguistic amendments and typographical corrections throughout the Product Information.”

B.6.10. CHMP-PRAC assessed procedures

Advate - octocog alfa -

EMA/H/C/000520/II/0092

Baxter AG, Rapporteur: Jan Mueller-Berghaus, PRAC Rapporteur: Brigitte Keller-Stanislawski, “Update of section 5.1 of the SmPC in order to add new data on immune tolerance induction (ITI). This update follows final results from study PASS-INT-004; this was a prospective, multi-centre, uncontrolled, open-label, non-interventional postauthorization safety surveillance study conducted to evaluate Advate in ITI therapy in subjects with moderate or severe hemophilia A (baseline factor VIII \leq 2%) and a high titer (> 5 BU) inhibitor to FVIII. The RMP version 16.0 has also been submitted.”

Dacogen - decitabine -

EMA/H/C/002221/II/0033, Orphan

Janssen-Cilag International N.V., Rapporteur: Alexandre Moreau, PRAC Rapporteur: Ghania Chamouni, “Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from paediatric study DACOGENAML2004 titled ‘Phase 1-2 Safety and Efficacy Study of DACOGEN in sequential administration with Cytarabine in children with relapsed or refractory acute myeloid leukemia’, provided as per the requirement of article 46. The RMP

version 3.1 (in line with the revision 2 of the RMP template) has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC to align the safety warning related to sodium excipient with the Annex to the revised European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The Package Leaflet is updated in accordance. Moreover, the contact details of the local representative in Slovenia have been updated in the Package Leaflet."

**Ovitrelle - choriogonadotropin alfa -
EMA/H/C/000320/11/0073/G**

Merck Serono Europe Limited, Rapporteur:
Paula Boudewina van Hennik, PRAC Rapporteur:
Menno van der Elst, "Update of section 4.8 of the SmPC in order to indicate that thromboembolism can also occur without the presence of ovarian hyperstimulation syndrome (OHSS). The package leaflet and risk management plan (RMP) (version 5.1) are updated accordingly.

The RMP is also updated to extend the important potential risk of 'misuse' to 'weight loss and anabolic growth promoting effect'. In addition, the marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the package leaflet, to make editorial changes in the product information and in the Annex A (list of authorised presentations). The MAH also took the opportunity to make some revisions in the RMP."

**Ozempic - semaglutide -
EMA/H/C/004174/11/0002/G**

Novo Nordisk A/S, Rapporteur: Johann Lodewijk Hillege, PRAC Rapporteur: Qun-Ying Yue

**Sivextro - tedizolid phosphate -
EMA/H/C/002846/11/0027**

Merck Sharp & Dohme Limited, Rapporteur:
Bruno Sepodes, PRAC Rapporteur: Dolores Montero Corominas, "Update of section 4.8 of the SmPC in order to add safety information based on the final results from Bayer study 16099, listed as Post-Authorisation Efficacy Study (PAES) in the RMP; this is a prospective, randomized, open-label, active-controlled,

multicenter study to evaluate the efficacy and safety of tedlizolid in Japanese patients with MRSA infections (skin and soft tissue infection [SSTI] and SSTI-related bacteremia).

The updated RMP version 4.0 is also being submitted, reflecting the new, second revision of the RMP template, issued by the EMA on 30 March 2017.”

Stayveer - bosentan -

EMA/H/C/002644/II/0023

Marklas Nederlands BV, Rapporteur: Alexandre Moreau, PRAC Rapporteur: Caroline Laborde, “Update of Annex II.D and the RMP following the submission of the final (13th) study report for the DUO Registry (a Category 3 non-interventional post-approval safety study and additional risk minimisation measure in the bosentan European Risk Management Plan).”

Tasigna - nilotinib -

EMA/H/C/000798/II/0095, Orphan

Novartis Europharm Limited, Rapporteur: Sinan B. Sarac, PRAC Rapporteur: Doris Stenver, “Update of section 4.6 of the SmPC following a review of information on pregnancy, lactation, female and male infertility and embryo-foetal developmental toxicity from the published literature, the MAH's safety database and preclinical safety data from reproductive animal studies. The Package Leaflet has been updated accordingly.

In addition, upon request by EMA, the MAH is proposing a potential update of Annex II section D (Key Elements of the Educational Material) in order to align the wording in Annex II with the current safety concerns outlined in the Tasigna EU RMP Education Materials.

Further, the MAH took the opportunity to implement minor editorial changes, corrections and/or additions in the SmPC and Package Leaflet based on data already submitted and assessed previously, including the alignment of section 4 of the Package Leaflet with section 4.8 of the SmPC and completeness of the list of excipients in SmPC section 6.1 and changes to SmPC sections 4.4 and 4.5. Finally, the MAH also took the opportunity to update the contact details in the list of local representatives in the Package Leaflet.”

Tracleer - bosentan -

EMEA/H/C/000401/II/0086

Actelion Registration Limited, Rapporteur:
Alexandre Moreau, PRAC Rapporteur: Caroline Laborde, "Update of Annex II.D and the RMP following the submission of the final (13th) study report for the DUO Registry (a Category 3 non-interventional post-approval safety study and additional risk minimisation measure in the bosentan European Risk Management Plan)."

Volibris - ambrisentan -**EMEA/H/C/000839/II/0054, Orphan**

Glaxo Group Ltd, Rapporteur: Concepcion Prieto Yerro, PRAC Rapporteur: Dolores Montero Corominas, "Update of sections 4.2 and 5.2 of the SmPC based on results of a juvenile nonclinical toxicology study. The Risk Management Plan version 7.5 (in version 2 of the RMP template) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct typographical errors including the rash frequency in section 4.8 of the SmPC and the date of renewal; and to introduce minor update in the braille section. Moreover, the MAH took the opportunity to propose combined version of the SmPCs for the different strengths."

WS1390**Levitra-EMEA/H/C/000475/WS1390/0062****Vivanza-****EMEA/H/C/000488/WS1390/0058**

Bayer AG, Lead Rapporteur: Concepcion Prieto Yerro, Lead PRAC Rapporteur: Dolores Montero Corominas, "Update of sections 4.4 and 4.8 of the SmPC to reflect data from two post-marketing observational studies indicating an increased risk of Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION) when using phosphodiesterase 5 (PDE5) inhibitors. The MAH is also terminating the Bayer NAION study 12912 and the RMP is updated accordingly to version 5.0.

In addition, the PI is brought in line with version 10.0 of the QRD template and the contact details of the Bulgarian local representative are updated in the Package Leaflets. The Package Leaflets for the 5 mg, 10 mg and 20 mg film-coated tablets strengths are combined into a single Package Leaflet and the PI for the 10 mg orodispersible tablet is updated for aspartame

and sorbitol, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. Some editorial amendments are also made to the PI."

B.6.11. PRAC assessed procedures

PRAC Led

Deltyba - delamanid -

EMA/H/C/002552/II/0030, Orphan

Otsuka Novel Products GmbH, Rapporteur: Greg Markey, PRAC Rapporteur: Julie Williams, PRAC-CHMP liaison: Greg Markey, "Update of the RMP (version 2.10), as requested by PRAC following the assessment of the Annual renewal to revise the risk re-categorisation justifications and lay language wording, as well as addition of clarifications to the described additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures and set up date of EU network of laboratories."

PRAC Led

Thymanax - agomelatine -

EMA/H/C/000916/II/0038

Servier (Ireland) Industries Ltd., Duplicate, Duplicate of Valdoxan, Rapporteur: Svein Rune Andersen, PRAC Rapporteur: Kristin Thorseng Kvande, PRAC-CHMP liaison: Svein Rune Andersen, "Submission of the final report from study CLE-20098-096 listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study: drug utilisation study (DUS) to assess effectiveness of risk-minimisation measures."

PRAC Led

Valdoxan - agomelatine -

EMA/H/C/000915/II/0039

Les Laboratoires Servier, Rapporteur: Svein Rune Andersen, PRAC Rapporteur: Kristin Thorseng Kvande, PRAC-CHMP liaison: Svein Rune Andersen, "Submission of the final report from study CLE-20098-096 listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study: drug utilisation study (DUS) to assess effectiveness of risk-minimisation measures."

PRAC Led

Viread - tenofovir disoproxil -

EMEA/H/C/000419/II/0186

Gilead Sciences International Limited,
Rapporteur: Joseph Emmerich, PRAC
Rapporteur: Caroline Laborde, PRAC-CHMP
liaison: Joseph Emmerich, "Submission of the final report from study GS-EU-174-1846, listed as a category 3 study in the RMP, in fulfilment of MEA 273. This is a 'Multicenter, Non-Interventional, Retrospective, Matched Cohort Study of Patients Monoinfected with Chronic Hepatitis B and with Moderate or Severe Renal Impairment Treated with Viread or Baraclude'."

B.6.12. CHMP-CAT assessed procedures

talimogene laherparepvec -**EMEA/H/C/002771/II/0020, ATMP**

, "Update of section 4.8 of the SmPC in order to add the new ADR 'hypersensitivity' with a frequency allocation of 'unknown'. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a minor editorial change in section 3 of the SmPC in order to clarify that the current description of the liquid applies to both strengths, and minor changes in section 4.4 of the SmPC and the Package Leaflet regarding sorbitol and sodium subsequent to the revised Annex to the EC guideline on excipients in the labelling (EMA/CHMP/302620/2017)."

B.6.13. CHMP-PRAC-CAT assessed procedures**B.6.14. PRAC assessed ATMP procedures****B.6.15. Unclassified procedures and worksharing procedures of type I variations**

WS1375**Actraphane-****EMEA/H/C/000427/WS1375/0075****Insulatard-****EMEA/H/C/000441/WS1375/0072****Mixtard-****EMEA/H/C/000428/WS1375/0076****Protaphane-****EMEA/H/C/000442/WS1375/0071**

Novo Nordisk A/S, Duplicate, Duplicate of Monotard (SRD), Ultratard (SRD), Lead

Rapporteur: Sinan B. Sarac

Opinion adopted on 26.04.2018.

WS1383

Renagel-

EMA/H/C/000254/WS1383/0110

Renvela-

EMA/H/C/000993/WS1383/0044

Sevelamer carbonate Zentiva-

EMA/H/C/003971/WS1383/0015

Genzyme Europe BV, Lead Rapporteur: Outi
Mäki-Ikola

WS1384/G

PegIntron-

EMA/H/C/000280/WS1384/0134/G

ViraferonPeg-

EMA/H/C/000329/WS1384/0127/G

Merck Sharp & Dohme Limited, Lead
Rapporteur: Filip Josephson

WS1385

Izba-EMA/H/C/002738/WS1385/0009

Travatan-

EMA/H/C/000390/WS1385/0058

Novartis Europharm Limited, Lead Rapporteur:
Concepcion Prieto Yerro

WS1386

Competact-

EMA/H/C/000655/WS1386/0070

Glubrava-

EMA/H/C/000893/WS1386/0057

Takeda Pharma A/S, Lead Rapporteur: Peter
Kiely

WS1388/G

Actos-

EMA/H/C/000285/WS1388/0079/G

Competact-

EMA/H/C/000655/WS1388/0069/G

Glubrava-

EMA/H/C/000893/WS1388/0056/G

Glustin-

EMA/H/C/000286/WS1388/0078/G

Tandemact-

EMA/H/C/000680/WS1388/0057/G

Takeda Pharma A/S, Lead Rapporteur: Peter
Kiely

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

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

B.7.2. Monthly Line listing for Type I variations

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

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

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

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

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

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

E. Annex E - EMEA CERTIFICATION OF PLASMA MASTER FILES

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

E.1. PMF Certification Dossiers:

E.1.1. Annual Update

E.1.2. Variations:

E.1.3. Initial PMF Certification:

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

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

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

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

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

G. ANNEX G

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

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

Qualification of Biomarkers:

HTA:

G.2. Ongoing procedures

G.3. PRIME

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

G.3.1. List of procedures concluding at 23-26 April 2018 CHMP plenary:

1. (SME); reduction of the duration, incidence and severity of severe oral mucositis (OM) induced by radiation therapy (RT), with or without systemic therapy.	The CHMP denied eligibility to PRIME and adopted the critical summary report.
2. Prevention and treatment of Gorlin syndrome	The CHMP denied eligibility to PRIME and adopted the critical summary report.
3. (SME); Treatment of Warm Antibody Autoimmune Haemolytic Anaemia who failed at least one prior treatment regimen	The CHMP denied eligibility to PRIME and adopted the critical summary report.

G.3.2. List of procedures starting in April 2018 for May 2018 CHMP adoption of outcomes

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