



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

27 February 2024  
EMA/PRAC/25440/2024 **Corr**<sup>1</sup>  
Human Medicines Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 27-30 November 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

### Health and safety information

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

### 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 scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the PRAC meeting highlights once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC 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, Rev. 1](#)).

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<sup>1</sup> Correction of PRAC recommendation for procedure 6.1.5 Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/202304

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## Table of contents

<b>1.</b>	<b>Introduction</b>	<b>14</b>
1.1.	Welcome and declarations of interest of members, alternates and experts .....	14
1.2.	Agenda of the meeting on 27-30 November 2023.....	14
1.3.	Minutes of the previous meeting on 23-26 October 2023 .....	14
<b>2.</b>	<b>EU referral procedures for safety reasons: urgent EU procedures</b>	<b>14</b>
2.1.	Newly triggered procedures .....	14
2.2.	Ongoing procedures .....	15
2.3.	Procedures for finalisation.....	15
<b>3.</b>	<b>EU referral procedures for safety reasons: other EU referral procedures</b>	<b>15</b>
3.1.	Newly triggered procedures .....	15
3.2.	Ongoing procedures .....	15
3.3.	Procedures for finalisation.....	15
3.3.1.	Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine – AERINAZE (CAP) – EMA/H/A-31/1526 .....	15
3.4.	Re-examination procedures.....	17
3.5.	Others .....	17
<b>4.</b>	<b>Signals assessment and prioritisation</b>	<b>17</b>
4.1.	New signals detected from EU spontaneous reporting systems .....	17
4.1.1.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) .....	17
4.2.	New signals detected from other sources .....	18
4.3.	Signals follow-up and prioritisation.....	18
4.3.1.	Axicabtagene ciloleucel – YESCARTA (CAP) - EMEA/H/C/004480/SDA/014 .....	18
4.3.2.	Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/SDA/022; Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/SDA/017 .....	18

4.3.3.	Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/SDA/030, BYETTA (CAP) - EMEA/H/C/000698/SDA/050; Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/SDA/010; Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/SDA/009; Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/SDA/017; liraglutide - SAXENDA (CAP) - EMEA/H/C/003780/SDA/020, VICTOZA (CAP) - EMEA/H/C/001026/SDA/040, XULTOPHY (CAP) - EMEA/H/C/002647/SDA/006; Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/SDA/008, RYBELSUS (CAP) - EMEA/H/C/004953/SDA/013, WEGOVY (CAP) - EMEA/H/C/005422/SDA/007;.....	19
4.3.4.	Pirfenidone - ESBRIET (CAP) - EMEA/H/C/002154/SDA/016, PIRFENIDONE AXUNIO (CAP), PIRFENIDONE VIATRIS (CAP); NAP.....	20
<b>4.4.</b>	<b>Variation procedure(s) resulting from signal evaluation .....</b>	<b>21</b>

## **5. Risk management plans (RMPs) 21**

<b>5.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>21</b>
5.1.1.	Aprocitentan - EMEA/H/C/006080.....	21
5.1.2.	Aumolertinib - EMEA/H/C/006069.....	21
5.1.3.	Aztreonam, Avibactam - EMEA/H/C/006113.....	21
5.1.4.	Flortaucipir ( <sup>18</sup> F) - EMEA/H/C/006064 .....	22
5.1.5.	Omecamtiv mecarbil - EMEA/H/C/006112.....	22
5.1.6.	Retifanlimab - EMEA/H/C/006194, Orphan.....	22
5.1.7.	Serplulimab - EMEA/H/C/006170, Orphan.....	22
5.1.8.	Sugemalimab - EMEA/H/C/006088.....	22
<b>5.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures.....</b>	<b>22</b>
<b>5.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures .....</b>	<b>22</b>
5.3.1.	Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/X/0089/G.....	22

## **6. Periodic safety update reports (PSURs) 23**

<b>6.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only .....</b>	<b>23</b>
6.1.1.	Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202305.....	23
6.1.2.	Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP) - PSUSA/00011035/202305.....	24
6.1.3.	Delamanid - DELTYBA (CAP) - PSUSA/00010213/202304 .....	25
6.1.4.	Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202304 .....	26
6.1.5.	Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/202304 .....	26
6.1.6.	Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/202304.....	27
6.1.7.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202304.....	28
6.1.8.	Meningococcal group A, C, W135, Y conjugate vaccine - MENQUADFI (CAP); NIMENRIX (CAP) - PSUSA/00010044/202304 .....	29
6.1.9.	Parecoxib - DYNASTAT (CAP) - PSUSA/00002314/202303 .....	29
6.1.10.	Tenofovir disoproxil - VIREAD (CAP) - PSUSA/00002892/202303 (with RMP) .....	30
6.1.11.	Tremelimumab - IMJUDO (CAP); TREMELIMUMAB ASTRAZENECA (CAP) - PSUSA/00011038/202304 .....	31

<b>6.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....</b>	<b>31</b>
6.2.1.	Tacrolimus - PROTOPIC (CAP); NAP - PSUSA/00002840/202303 .....	32
<b>6.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>32</b>
6.3.1.	Aceclofenac (NAP) - PSUSA/00000022/202303.....	32
6.3.2.	Ciprofloxacin (NAP) - PSUSA/00000775/202304 .....	33
6.3.3.	Clarithromycin (NAP) - PSUSA/00000788/202304.....	34
6.3.4.	Cytarabine (NAP) - PSUSA/00000911/202303 .....	35
6.3.5.	Fentanyl (NAP) - PSUSA/00001370/202304 .....	36
6.3.6.	Gentamicin (NAP) - PSUSA/00009159/202303 .....	36
6.3.7.	Isotretinoin (NAP) - PSUSA/00010488/202305.....	37
6.3.8.	Nortriptyline (NAP) - PSUSA/00002192/202303.....	38
6.3.9.	Piroxicam (NAP) - PSUSA/00002438/202304 .....	39
6.3.10.	Pravastatin (NAP) - PSUSA/00002500/202303 .....	39
6.3.11.	Racecadotril (NAP) - PSUSA/00002602/202303 .....	40
6.3.12.	Venlafaxine (NAP) - PSUSA/00003104/202305.....	41
<b>6.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>42</b>
<b>6.5.</b>	<b>Variation procedure(s) resulting from PSUSA evaluation .....</b>	<b>42</b>
<b>6.6.</b>	<b>Expedited summary safety reviews .....</b>	<b>42</b>
<b>7.</b>	<b>Post-authorisation safety studies (PASS)</b>	<b>42</b>
<b>7.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>42</b>
<b>7.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>42</b>
<b>7.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s).....</b>	<b>42</b>
7.3.1.	Valproate (NAP) - EMEA/H/N/PSR/J/0043 .....	42
<b>7.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s).....</b>	<b>43</b>
7.4.1.	Hepatitis B surface antigen (rDNA) - HEPLISAV B (CAP) - EMEA/H/C/005063/II/0031 .....	43
<b>7.5.</b>	<b>Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....</b>	<b>44</b>
<b>7.6.</b>	<b>Others .....</b>	<b>44</b>
<b>7.7.</b>	<b>New Scientific Advice .....</b>	<b>44</b>
<b>7.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>44</b>
<b>7.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>44</b>
<b>8.</b>	<b>Renewals of the marketing authorisation, conditional renewal and annual reassessments</b>	<b>44</b>
<b>8.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>44</b>
<b>8.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>44</b>
<b>8.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>44</b>

<b>9.</b>	<b>Product related pharmacovigilance inspections</b>	<b>45</b>
9.1.	List of planned pharmacovigilance inspections.....	45
9.2.	Ongoing or concluded pharmacovigilance inspections.....	45
9.3.	Others .....	45
<b>10.</b>	<b>Other safety issues for discussion requested by CHMP or EMA</b>	<b>45</b>
10.1.	Safety related variations of the marketing authorisation.....	45
10.2.	Timing and message content in relation to Member States' safety announcements .....	45
10.3.	Other requests.....	45
10.4.	Scientific Advice .....	45
<b>11.</b>	<b>Other safety issues for discussion requested by the Member States</b>	<b>45</b>
11.1.	Safety related variations of the marketing authorisation.....	45
11.2.	Other requests.....	45
<b>12.</b>	<b>Organisational, regulatory and methodological matters</b>	<b>46</b>
12.1.	Mandate and organisation of PRAC.....	46
12.1.1.	PRAC membership .....	46
12.1.2.	Vote by proxy .....	46
12.1.3.	PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2023 .....	46
12.2.	Coordination with EMA Scientific Committees or CMDh-v .....	46
12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups .....	46
12.4.	Cooperation within the EU regulatory network.....	46
12.4.1.	Health threats and EMA Emergency Task Force (ETF) activities - update.....	46
12.5.	Cooperation with International Regulators.....	46
12.6.	Contacts of PRAC with external parties and interaction with the Interested Parties to the Committee.....	47
12.7.	PRAC work plan .....	47
12.7.1.	PRAC work plan 2024.....	47
12.8.	Planning and reporting .....	47
12.8.1.	EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2023 and predictions.....	47
12.8.2.	PRAC workload statistics – Q3 2023 .....	47
12.9.	Pharmacovigilance audits and inspections .....	47
12.9.1.	Pharmacovigilance systems and their quality systems .....	47
12.9.2.	Pharmacovigilance inspections .....	47
12.9.3.	Pharmacovigilance audits.....	47
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list .....	48
12.10.1.	Periodic safety update reports .....	48

12.10.2.	Granularity and Periodicity Advisory Group (GPAG) .....	48
12.10.3.	PSURs repository .....	48
12.10.4.	Union reference date list – consultation on the draft list .....	48
<b>12.11.</b>	<b>Signal management .....</b>	<b>48</b>
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group .....	48
<b>12.12.</b>	<b>Adverse drug reactions reporting and additional monitoring .....</b>	<b>49</b>
12.12.1.	Management and reporting of adverse reactions to medicinal products .....	49
12.12.2.	Additional monitoring .....	49
12.12.3.	List of products under additional monitoring – consultation on the draft list .....	49
<b>12.13.</b>	<b>EudraVigilance database .....</b>	<b>49</b>
12.13.1.	Activities related to the confirmation of full functionality .....	49
<b>12.14.</b>	<b>Risk management plans and effectiveness of risk minimisations .....</b>	<b>49</b>
12.14.1.	Risk management systems .....	49
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations .....	49
<b>12.15.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>49</b>
12.15.1.	Post-authorisation Safety Studies – imposed PASS .....	49
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS .....	49
<b>12.16.</b>	<b>Community procedures .....</b>	<b>49</b>
12.16.1.	Referral procedures for safety reasons .....	49
12.16.2.	Referral procedures - minor revision to the (Co-)Rapporteur assessment report templates .....	50
<b>12.17.</b>	<b>Renewals, conditional renewals, annual reassessments .....</b>	<b>50</b>
<b>12.18.</b>	<b>Risk communication and transparency .....</b>	<b>50</b>
12.18.1.	Public participation in pharmacovigilance .....	50
12.18.2.	Safety communication .....	50
<b>12.19.</b>	<b>Continuous pharmacovigilance .....</b>	<b>50</b>
12.19.1.	Incident management .....	50
<b>12.20.</b>	<b>Impact of pharmacovigilance activities .....</b>	<b>50</b>
12.20.1.	Implementation of EU risk minimisation measures for medicinal products in clinical guidelines (SC01/EMA/2020/46/TDA/L4.02) - PRAC Sponsor’s critical appraisal .....	50
<b>12.21.</b>	<b>Others .....</b>	<b>50</b>
12.21.1.	EMA-HMA catalogues of real-world data sources and non-interventional studies .....	50
12.21.2.	Q&A on ‘What is the day zero for ICSRs described in physical/hard copy local journals?’ published in January 2023 - proposal for update .....	51
12.21.3.	Real World Evidence and Data analysis and real-world interrogation network (DARWIN EU®) – quarterly update .....	51
12.21.4.	Real World Evidence and Data analysis and real-world interrogation network (DARWIN EU®) - results of a drug utilization study of prescription opioids .....	51
12.21.5.	Stakeholder engagement for risk minimisation - PRAC Risk Minimisation Alliance (PRISMA) - pilot report for 2022-2023 and planning for 2024 .....	51

<b>13.</b>	<b>Any other business</b>	<b>52</b>
<b>14.</b>	<b>Annex I – Signals assessment and prioritisation</b>	<b>52</b>
<b>14.1.</b>	<b>New signals detected from EU spontaneous reporting systems</b>	<b>52</b>
14.1.1.	Brolucizumab – BEOVU (CAP)	52
14.1.2.	Doxycycline (NAP)	52
14.1.3.	Ethambutol (NAP)	53
14.1.4.	Glatiramer (NAP)	53
<b>14.2.</b>	<b>New signals detected from other sources</b>	<b>53</b>
14.2.1.	Afatinib - GIOTRIF (CAP)	53
<b>15.</b>	<b>Annex I – Risk management plans</b>	<b>53</b>
<b>15.1.</b>	<b>Medicines in the pre-authorisation phase</b>	<b>53</b>
15.1.1.	Apremilast - EMEA/H/C/006208	53
15.1.2.	Buprenorphine - EMEA/H/C/006188	53
15.1.3.	Nintedanib - EMEA/H/C/006179	54
15.1.4.	Ustekinumab - EMEA/H/C/006183	54
<b>15.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures</b>	<b>54</b>
15.2.1.	Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0071	54
15.2.2.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0043	54
15.2.3.	Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0090	54
15.2.4.	Doxorubicin - CAELYX PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/000089/II/0107	55
15.2.5.	Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS2569/0059; IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/WS2569/0019; PROCORALAN (CAP) - EMEA/H/C/000597/WS2569/0058	55
15.2.6.	Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0127	55
15.2.7.	Sildenafil - REVATIO (CAP) - EMEA/H/C/000638/II/0107	55
15.2.8.	Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/II/0047	55
<b>15.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures</b>	<b>56</b>
15.3.1.	Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/II/0010	56
15.3.2.	Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0044, Orphan	56
15.3.3.	Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0051	56
15.3.4.	Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/WS2467/0051; FOSAVANCE (CAP) - EMEA/H/C/000619/WS2467/0054; VANTAVO (CAP) - EMEA/H/C/001180/WS2467/0041	56
15.3.5.	Alpelisib - PIQRAY (CAP) - EMEA/H/C/004804/II/0022/G	57
15.3.6.	Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0081	57
15.3.7.	Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0082	57
15.3.8.	Bezlotoxumab - ZINPLAVA (CAP) - EMEA/H/C/004136/II/0037	58
15.3.9.	Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0035/G, Orphan	58



15.3.10.	Ciltacabtagene autoleucl - CARVYKTI (CAP) - EMEA/H/C/005095/II/0021, Orphan .....	58
15.3.11.	Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0027 .....	59
15.3.12.	Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - EMEA/H/C/004917/II/0014/G .....	59
15.3.13.	Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0063.....	59
15.3.14.	Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58) - EMEA/H/W/002320/II/0016.....	60
15.3.15.	Human fibrinogen, human thrombin - VERASEAL (CAP) - EMEA/H/C/004446/II/0027.....	60
15.3.16.	Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0087 .....	60
15.3.17.	Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0038, Orphan .....	61
15.3.18.	Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0026, Orphan .....	61
15.3.19.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0039, Orphan.	61
15.3.20.	Maralixibat - LIVMARLI (CAP) - EMEA/H/C/005857/II/0003/G, Orphan .....	61
15.3.21.	Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/II/0017/G, Orphan .....	62
15.3.22.	Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0053.....	62
15.3.23.	Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0017 .....	62
15.3.24.	Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0045.....	63
15.3.25.	Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/X/0042/G .....	63
15.3.26.	Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0010/G.....	64
15.3.27.	Teriflunomide - TERIFLUNOMIDE ACCORD (CAP) - EMEA/H/C/005960/X/0002 .....	64
15.3.28.	Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0063 .....	64

## **16. Annex I - Periodic safety update reports (PSURs) 64**

<b>16.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only .....</b>	<b>65</b>
16.1.1.	Abaloparatide - ELADYNOS (CAP) - PSUSA/00011029/202304 .....	65
16.1.2.	Alogliptin; alogliptin, metformin; alogliptin, pioglitazone - INCRESYNC (CAP); VIPDOMET (CAP); VIPIDIA (CAP) - PSUSA/00010061/202304.....	65
16.1.3.	Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202304 .....	65
16.1.4.	Asciminib - SCEMBLIX (CAP) - PSUSA/00011008/202304 .....	65
16.1.5.	Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/202304.....	65
16.1.6.	Bupivacaine - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202304 .....	65
16.1.7.	Canagliflozin; canagliflozin, metformin - INVOKANA (CAP); VOKANAMET (CAP) - PSUSA/00010077/202303 (with RMP) .....	66
16.1.8.	Capmatinib - TABRECTA (CAP) - PSUSA/00011022/202305 .....	66
16.1.9.	Cholera vaccine (inactivated, oral) - DUKORAL (CAP) - PSUSA/00000730/202304 .....	66
16.1.10.	Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - PSUSA/00010449/202305 .....	66
16.1.11.	Conestat alfa - RUCONEST (CAP) - PSUSA/00000873/202304 .....	66
16.1.12.	Dimethyl fumarate, diroximel fumarate - TECFIDERA (CAP); VUMERITY (CAP) - PSUSA/00010143/202303 .....	66
16.1.13.	Dolutegravir, rilpivirine - JULUCA (CAP) - PSUSA/00010689/202305.....	66



16.1.14.	Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202304.....	67
16.1.15.	Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202305 .	67
16.1.16.	Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/202304.....	67
16.1.17.	Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/202304.....	67
16.1.18.	Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202305.....	67
16.1.19.	Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202304.....	67
16.1.20.	Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202304.....	67
16.1.21.	Fulvestrant - FASLODEX (CAP) - PSUSA/00001489/202304 .....	68
16.1.22.	Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202304 .....	68
16.1.23.	Golimumab - SIMPONI (CAP) - PSUSA/00001560/202304 .....	68
16.1.24.	Hepatitis B surface antigen, CpG 1018 adjuvant - HEPLISAV B (CAP) - PSUSA/00010919/202305 .....	68
16.1.25.	Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/202304 .....	68
16.1.26.	Linzagolix choline - YSELY (CAP) - PSUSA/00010998/202305 .....	68
16.1.27.	Loncastuximab tesirine - ZYNLONTA (CAP) - PSUSA/00011027/202304.....	68
16.1.28.	Mitotane - LYSODREN (CAP) - PSUSA/00002075/202304.....	69
16.1.29.	Nintedanib - OFEV (CAP) - PSUSA/00010319/202304 .....	69
16.1.30.	Nirsevimab - BEYFORTUS (CAP) - PSUSA/00011026/202304.....	69
16.1.31.	Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202304 .....	69
16.1.32.	Pegcetacoplan - ASPAVELI (CAP) - PSUSA/00010974/202305 .....	69
16.1.33.	Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202304.....	69
16.1.34.	Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202304 .....	69
16.1.35.	Recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live) - ERVEBO (CAP) - PSUSA/00010834/202305 .....	70
16.1.36.	Remdesivir (Veklury) - VEKLURY (CAP) - PSUSA/00010840/202305.....	70
16.1.37.	Ripretinib - QINLOCK (CAP) - PSUSA/00010962/202305 .....	70
16.1.38.	Sacituzumab govitecan - TRODELVY (CAP) - PSUSA/00010959/202304.....	70
16.1.39.	Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202305 .....	70
16.1.40.	Somatrogon - NGENLA (CAP) - PSUSA/00010982/202304 .....	70
16.1.41.	Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202305 .....	70
16.1.42.	Tirzepatide - MOUNJARO (CAP) - PSUSA/00011019/202305.....	71
16.1.43.	Tixagevimab, cilgavimab - EVUSHELD (CAP) - PSUSA/00010992/202305 .....	71
16.1.44.	Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202304 .....	71
16.1.45.	Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202305 .....	71
16.1.46.	Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202305 .....	71
<b>16.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....</b>	<b>71</b>

16.2.1.	Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB FRESENIUS KABI (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/202304 .....	71
16.2.2.	Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP); NAP - PSUSA/00001799/202304 .....	72
16.2.3.	Somatropin - NUTROPINAQ (CAP); OMNITROPE (CAP); NAP - PSUSA/00002772/202303..	72
<b>16.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>72</b>
16.3.1.	Acarbose (NAP) - PSUSA/00000017/202303 .....	72
16.3.2.	Benzyl nicotinate, camphor, dimethyl sulfoxide, nonivamide, turpentine oil; nicoboxil, nonivamide (NAP) - PSUSA/00010584/202303.....	72
16.3.3.	Deproteinised hemoderivative of calf blood; deproteinised hemoderivative of calf blood, macrogol 400 (NAP) - PSUSA/00010600/202303.....	72
16.3.4.	Doxylamine (NAP) - PSUSA/00001174/202304.....	72
16.3.5.	Dronabinol, cannabidiol (NAP) - PSUSA/00010844/202304 .....	73
16.3.6.	Enalapril (NAP) - PSUSA/00001211/202303 .....	73
16.3.7.	Epinephrine, mepivacaine hydrochloride; mepivacaine, norepinephrine; mepivacaine (NAP) - PSUSA/00001979/202303 .....	73
16.3.8.	Estradiol; estradiol, prednisolone (NAP) - PSUSA/00010441/202304 .....	73
16.3.9.	Foscarnet (NAP) - PSUSA/00001472/202303 .....	73
16.3.10.	Ivabradine, metoprolol (NAP) - PSUSA/00010381/202304 .....	73
16.3.11.	Lavender oil (NAP) - PSUSA/00010810/202304 .....	73
16.3.12.	Methylphenobarbital (NAP) - PSUSA/00002025/202303.....	74
16.3.13.	Mometasone furoate, olopatadine (NAP) - PSUSA/00010957/202304 .....	74
16.3.14.	Ofloxacin (NAP) - PSUSA/00002203/202304 .....	74
16.3.15.	Pimecrolimus (NAP) - PSUSA/00002411/202303 .....	74
16.3.16.	Piribedil (NAP) - PSUSA/00002436/202303 .....	74
16.3.17.	Porfimer (NAP) - PSUSA/00010332/202304 .....	74
16.3.18.	Rifamycin (NAP) - PSUSA/00002641/202304 .....	74
16.3.19.	Sodium tetradecyl sulphate (NAP) - PSUSA/00002767/202304.....	75
16.3.20.	Triamcinolone (NAP) - PSUSA/00010292/202303 .....	75
<b>16.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>75</b>
16.4.1.	Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/LEG 057 .....	75
<b>16.5.</b>	<b>Variation procedure(s) resulting from PSUSA evaluation .....</b>	<b>75</b>
<b>16.6.</b>	<b>Expedited summary safety reviews .....</b>	<b>75</b>
<b>17.</b>	<b>Annex I – Post-authorisation safety studies (PASS) .....</b>	<b>75</b>
<b>17.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>75</b>
17.1.1.	Ketoconazole - Ketoconazole HRA (CAP) - EMEA/H/C/PSA/S/0109 .....	75
17.1.2.	Selumetinib - KOSELUGO (CAP) - EMEA/H/C/PSA/S/0108.....	76
17.1.3.	Valproate (NAP) - EMEA/H/N/PSP/J/0074.8 .....	76

<b>17.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s)</b>	<b>76</b>
17.2.1.	Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 001.2	76
17.2.2.	Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.10	76
17.2.3.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 015.1	77
17.2.4.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 016.1	77
17.2.5.	Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 002.3	77
17.2.6.	Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004.2	77
17.2.7.	Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.10	77
17.2.8.	Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 007.1	78
17.2.9.	Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 077	78
17.2.10.	Daridorexant - QUVIVIQ (CAP) - EMEA/H/C/005634/MEA 003.1	78
17.2.11.	Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/MEA 011	78
17.2.12.	Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 002.2	78
17.2.13.	Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 004.2	79
17.2.14.	Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005.2	79
17.2.15.	Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSSVO (CAP) - EMEA/H/C/006027/MEA 002	79
17.2.16.	Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 009.1	79
17.2.17.	Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 005	79
17.2.18.	Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 005	80
17.2.19.	Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.5	80
17.2.20.	Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005.3	80
17.2.21.	Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.4	80
17.2.22.	Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 016.2	81
17.2.23.	Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 030	81
<b>17.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s)</b>	<b>81</b>
17.3.1.	Levofloxacin – QUINSAIR (CAP) - EMEA/H/C/PSR/S/0046	81
<b>17.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s)</b>	<b>81</b>
17.4.1.	Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/II/0054	81
17.4.2.	Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/WS2571/0055; Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/WS2571/0082; Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/WS2571/0076	82
17.4.3.	Filgrastim - NIVESTIM (CAP) - EMEA/H/C/001142/II/0074/G	82
17.4.4.	Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0117/G	82
17.4.5.	Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0241	82
17.4.6.	Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0053	83
17.4.7.	Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0199	83

<b>17.5.</b>	<b>Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....</b>	<b>83</b>
17.5.1.	Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.9 .....	83
17.5.2.	Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 118 .....	83
17.5.3.	Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.4.....	84
17.5.4.	Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.11 .....	84
17.5.5.	Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.8.....	84
17.5.6.	Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.8.....	84
17.5.7.	Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.6.....	84
17.5.8.	Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/SOB 004.....	85
17.5.9.	Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.4 .....	85
<b>17.6.</b>	<b>Others .....</b>	<b>85</b>
<b>17.7.</b>	<b>New Scientific Advice .....</b>	<b>85</b>
<b>17.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>85</b>
<b>17.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>85</b>
<b>18.</b>	<b>Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments</b>	<b>85</b>
<b>18.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>86</b>
18.1.1.	Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0066 (without RMP) .....	86
18.1.2.	Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0042 (without RMP) .....	86
18.1.3.	Eladocagene exuparvovec - UPSTAZA (CAP) - EMEA/H/C/005352/S/0017 (without RMP)..	86
18.1.4.	Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0057 (without RMP) .....	86
18.1.5.	Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0081 (without RMP) .....	86
18.1.6.	Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0095 (without RMP) .....	86
18.1.7.	Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0090 (without RMP) .....	87
<b>18.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>87</b>
18.2.1.	Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0070 (with RMP) .....	87
18.2.2.	Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0058 (with RMP) .....	87
18.2.3.	Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0054 (without RMP) .....	87
18.2.4.	Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/R/0013 (without RMP).....	87
18.2.5.	Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0026 (without RMP).....	87
<b>18.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>87</b>
18.3.1.	Ambrisentan - AMBRISENTAN MYLAN (CAP) - EMEA/H/C/004985/R/0009 (without RMP) ..	87
18.3.2.	Avatrombopag - DOPTelet (CAP) - EMEA/H/C/004722/R/0018 (without RMP) .....	88
18.3.3.	Pegfilgrastim - GRASUSTEK (CAP) - EMEA/H/C/004556/R/0014 (with RMP) .....	88
18.3.4.	Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/R/0022 (without RMP) .....	88

<b>19.</b>	<b>Annex II – List of participants</b>	<b>88</b>
<b>20.</b>	<b>Annex III - List of acronyms and abbreviations</b>	<b>97</b>
<b>21.</b>	<b>Explanatory notes</b>	<b>97</b>

## 1. Introduction

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

The Chair opened the meeting by welcoming all participants. The meeting was held in-person.

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<sup>2</sup> and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

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 ([EMA/PRAC/567515/2012 Rev.3](#)). All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair welcomed the new member(s) and alternate(s) and thanked the departing members/alternates for their contributions to the Committee.

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

### 1.2. Agenda of the meeting on 27-30 November 2023

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat as applicable.

### 1.3. Minutes of the previous meeting on 23-26 October 2023

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 23-26 October 2023 were published on the EMA website on 10 January 2024 ([EMA/PRAC/565432/2023](#)).

## 2. EU referral procedures for safety reasons: urgent EU procedures

### 2.1. Newly triggered procedures

None

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<sup>2</sup> No alternates for COMP

## 2.2. Ongoing procedures

None

## 2.3. Procedures for finalisation

None

## 3. EU referral procedures for safety reasons: other EU referral procedures

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

None

### 3.3. Procedures for finalisation

3.3.1. Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine – AERINAZE (CAP) – EMA/H/A-31/1526

Applicant(s): various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Maia Uusküla

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for pseudoephedrine-containing products following the assessment of the PSUR single assessment (PSUSA) procedure on ibuprofen/pseudoephedrine (PSUSA/00001711/202207) concluded in February 2023. The data submitted by the MAHs within the PSUSA procedure



suggested a causal relationship between posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS) and pseudoephedrine use, based on the compatible and suggestive time to onset, the biological plausibility and the lack of alternative aetiologies for some patients without any risk factors. For further background, see [PRAC minutes January 2023](#), [PRAC minutes February 2023](#), [PRAC minutes May 2023](#), [PRAC minutes September 2023](#) and [PRAC minutes October 2023](#)<sup>3</sup>. A final assessment of the data submitted was performed by the Rapporteurs according to the agreed timetable.

## Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC reviewed the totality of the data available for pseudoephedrine-containing medicinal products in relation to the risks of PRES and RCVS in the context of the overall safety profile of the medicines. These data included the responses submitted in writing by the MAHs, available literature and the outcome of the consultation with an ad-hoc expert group. PRAC also noted the intervention by a third party.

PRAC concluded that the serious reactions of PRES and RCVS are important identified risks associated with the use of pseudoephedrine-containing medicinal products.

PRAC considered that the data reviewed raise concerns about the use of pseudoephedrine-containing medicinal products in patients with severe or uncontrolled hypertension and in patients with severe acute or chronic kidney disease/renal failure, and concluded that the use of pseudoephedrine-containing medicinal products should be contraindicated in these patient populations.

Moreover, PRAC considered there is a need to update the product information of these products to reflect the current knowledge on the occurrence of these reactions and the measures to follow in case of symptoms or signs of PRES or RCVS.

As a consequence, PRAC considered that the benefit-risk balance of all pseudoephedrine-containing medicinal products remains favourable subject to the agreed amendments to the product information and other risk minimisation measures.

## Summary of recommendation(s)/conclusions

- PRAC adopted, by majority, a recommendation to vary<sup>4</sup> the terms of the marketing authorisations for pseudoephedrine-containing medicines to be considered by CHMP for an opinion.
- PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Thirty-two members voted in favour of the recommendation whilst one<sup>5</sup> member had a divergent view. The Norwegian PRAC alternate agreed with the recommendation.

Post-meeting note 1: the press release entitled 'PRAC recommends measures to minimise the risk of serious side effects with medicines containing pseudoephedrine' ([EMA/535476/2023](#)) was published on the EMA website on 01 December 2023.

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<sup>3</sup> Held 25-28 September 2023

<sup>4</sup> Update of SmPC sections 4.3, 4.4 and 4.8. The labelling and package leaflet are updated accordingly

<sup>5</sup> Tiphaine Vaillant

### 3.4. Re-examination procedures<sup>6</sup>

None

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>7</sup>

### 4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

#### 4.1.1. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP)

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Signal of intracranial pressure increased

EPITT 20000 – New signal

#### Background

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

During routine signal detection activities, a signal of intracranial pressure increased was identified by EMA, based on 30 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

#### Discussion

Having considered the available evidence from case reports in EudraVigilance, PRAC agreed that further evaluation on the signal of intracranial pressure increased is warranted and agreed to extend the signal to other medicinal products of the cystic fibrosis transmembrane conductance regulator (CFTR) modulators class indicated for the treatment of cystic fibrosis including Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symkevi (tezacaftor/ivacaftor).

#### Summary of recommendation(s)

- The MAH for Kaftrio (ivacaftor/tezacaftor/elexacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symkevi (tezacaftor/ivacaftor) should submit to EMA, within 60 days, a cumulative review of cases of intracranial pressure increased, including cases of idiopathic intracranial hypertension from the published literature, data from spontaneous reports and reports from studies, as well as a discussion on possible

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<sup>6</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

<sup>7</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

biological plausibility and mechanism of this association along with a discussion on the possibility of a class effect of CFTR modulators. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

See Annex I 14.2.

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Axicabtagene ciloleucel – YESCARTA (CAP) - EMEA/H/C/004480/SDA/014

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Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Karin Erneholt

Scope: Signal of progressive multifocal leukoencephalopathy (PML)

EPITT 19940 – follow up to July 2023

#### Background

For background information, see [PRAC minutes July 2023](#).

The MAH replied to the request for information on the signal of PML and the responses were assessed by the Rapporteur.

#### Discussion

Having considered the available evidence in EudraVigilance and literature, as well as the response from the MAH, PRAC agreed to add reactivation of JC virus leading to PML as a warning in the product information, and to include PML in the PSUR list of safety concerns as an important potential risk, while inclusion of this risk in the list of safety concerns in the RMP is not considered warranted at this stage.

#### Summary of recommendation(s)

- The MAH for Yescarta (axicabtagene ciloleucel) should submit to EMA, within 60 days, a variation to amend<sup>8</sup> the product information.
- In the next PSURs, the MAH should provide an evaluation of new information regarding this risk of PML from all sources, including the post-authorisation safety study (PASS) KT-EU-471-0117.

For the full PRAC recommendation, see [EMA/PRAC/539397/2023](#) published on 05 January 2024 on the EMA website.

### 4.3.2. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/SDA/022; Trametinib - MEKINIST (CAP) - EMEA/H/C/002643/SDA/017

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Applicant: Novartis Europharm Limited

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<sup>8</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly.

PRAC Rapporteur: David Olsen

Scope: Signal of peripheral neuropathy

EPITT 19947 – follow up to July 2023

## Background

For background information, see [PRAC minutes July 2023](#).

The MAH replied to the request for information on the signal of peripheral neuropathy and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence in EudraVigilance and literature, as well as the response from the MAH, PRAC agreed that there is sufficient evidence to establish a causal relationship between use of dabrafenib and trametinib with peripheral neuropathy. Therefore, PRAC agreed to add peripheral neuropathy (including sensory and motor neuropathy) as an undesirable effect to the product information of both dabrafenib and trametinib with a frequency 'common'.

## Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should submit to EMA, within 60 days, a variation to amend<sup>9</sup> the product information.
- In the next PSUR<sup>10</sup>, the MAH should provide a cumulative review of cases of Guillain-Barre Syndrome and related terms (including but not limited to immune-mediated neuropathies and autoimmune neuropathies, demyelinating neuropathy, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy), associated with dabrafenib and trametinib when used in monotherapy and in combination therapy, from all sources including the published literature, data from spontaneous reports and reports from studies, as well as a discussion on possible biological plausibility and mechanism of this association. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.

For the full PRAC recommendation, see [EMA/PRAC/539397/2023](#) published on 05 January 2024 on the EMA website.

4.3.3. [Exenatide - BYDUREON \(CAP\) - EMEA/H/C/002020/SDA/030](#), [BYETTA \(CAP\) - EMEA/H/C/000698/SDA/050](#); [Dulaglutide - TRULICITY \(CAP\) - EMEA/H/C/002825/SDA/010](#); [Insulin glargine, lixisenatide - SULIQUA \(CAP\) - EMEA/H/C/004243/SDA/009](#); [Lixisenatide - LYXUMIA \(CAP\) - EMEA/H/C/002445/SDA/017](#); [liraglutide - SAXENDA \(CAP\) - EMEA/H/C/003780/SDA/020](#), [VICTOZA \(CAP\) - EMEA/H/C/001026/SDA/040](#), [XULTOPHY \(CAP\) - EMEA/H/C/002647/SDA/006](#); [Semaglutide - OZEMPIC \(CAP\) - EMEA/H/C/004174/SDA/008](#), [RYBELSUS \(CAP\) - EMEA/H/C/004953/SDA/013](#), [WEGOVY \(CAP\) - EMEA/H/C/005422/SDA/007](#);

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Applicant: AstraZeneca AB (Bydureon, Byetta), Eli Lilly Nederland B.V. (Trulicity, Novo Nordisk A/S (Ozempic, Rybelsus, Saxenda, Victoza, Wegovy, Xultophy), Sanofi Winthrop Industrie (Lyxumia, Suliqua)

<sup>9</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly.

<sup>10</sup> Data lock point: 29 May 2024

PRAC Rapporteur: Menno van der Elst

Scope: Signal of suicidal ideation and self-injurious ideation

EPITT 19946 – follow up to July 2023

### **Background**

For background information, see [PRAC minutes July 2023](#).

The MAHs replied to the request for information on the signal of suicidal ideation and self-injurious ideation and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence from EudraVigilance and the literature, as well as the responses from the MAHs, PRAC considered that the current evidence is insufficient to conclude on a causal relationship between treatment with glucagon-like peptide 1 (GLP-1) receptor agonists and suicidal ideation at this stage, and that further evaluation of the signal is needed.

### **Summary of recommendation(s)**

- The MAHs for Ozempic, Rybelsus and Wegovy products containing semaglutide, for Victoza and Saxenda products containing liraglutide, for Xultophy (insulin degludec, liraglutide), for Byetta and Bydureon products containing exenatide, for Lyxumia (lixisenatide), for Suliqua (insulin glargine, lixisenatide) and for Trulicity (dulaglutide) should submit to EMA, within 30 days, data from the clinical trials on the proportion of subjects not using antidepressants at baseline but receiving treatment with antidepressants during the study only for the subjects reported adverse events of depression and/or suicidal ideation, as well as some clarifications on the already submitted data as warranted.
- PRAC will assess the responses within a 90-day timetable.

Post-meeting note: PRAC adopted an updated list of questions to the MAH via written procedure (21 December 2023).

For the full PRAC recommendation, see [EMA/PRAC/539397/2023](#) published on 05 January 2024 on the EMA website.

#### **4.3.4. [Pirfenidone – ESBRIET \(CAP\) - EMEA/H/C/002154/SDA/016, PIRFENIDONE AXUNIO \(CAP\), PIRFENIDONE VIATRIS \(CAP\); NAP](#)**

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Applicant: Axunio Pharma GmbH (Pirfenidone Axunio), Roche Registration GmbH (Esbriet), Viatris Limited (Pirfenidone Viatris), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19920 – follow up to May 2023

### **Background**

For background information, see [PRAC minutes May 2023](#).

The MAH replied to the request for information on the signal of DRESS and the responses were assessed by the Rapporteur.

## Discussion

Having considered the known association of pirfenidone with severe skin reactions and the available new evidence on DRESS, including the responses submitted by the MAH Roche, PRAC agreed that there is sufficient evidence to establish a causal relationship between pirfenidone and DRESS. Therefore, PRAC agreed to add DRESS as a warning and as an undesirable effect to the product information of Esbriet, Pirfenidone axunio and Pirfenidone Viatris products containing pirfenidone with a frequency 'not known'.

### Summary of recommendation(s)

- The MAHs for pirfenidone-containing products, should submit to EMA, within 90 days, a variation to amend<sup>11</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/539397/2023](#) published on 05 January 2024 on the EMA website.

## 4.4. Variation procedure(s) resulting from signal evaluation

None

## 5. Risk management plans (RMPs)

### 5.1. Medicines in the pre-authorisation phase

PRAC provided advice to CHMP on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>).

See also Annex I 15.1.

#### 5.1.1. Aprocitentan - EMEA/H/C/006080

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Scope: Treatment of resistant hypertension

#### 5.1.2. Aumolertinib - EMEA/H/C/006069

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Scope: Treatment of non-small cell lung cancer

#### 5.1.3. Aztreonam, Avibactam - EMEA/H/C/006113

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Scope (accelerated assessment): Treatment of infections (complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) and complicated urinary tract infection (cUTI), including pyelonephritis, and aerobic Gram-negative infections with limited treatment options

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<sup>11</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

#### 5.1.4. Flortaucipir (<sup>18</sup>F) - EMEA/H/C/006064

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Scope: Indicated for Positron Emission Tomography (PET) imaging of the brain

#### 5.1.5. Omecamtiv mecarbil - EMEA/H/C/006112

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Scope: Treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction less than 30%

#### 5.1.6. Retifanlimab - EMEA/H/C/006194, Orphan

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Applicant: Incyte Biosciences Distribution B.V.

Scope: Treatment of Merkel cell carcinoma (MCC)

#### 5.1.7. Serplulimab - EMEA/H/C/006170, Orphan

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Applicant: Henlius Europe GmbH

Scope: First-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

#### 5.1.8. Sugemalimab - EMEA/H/C/006088

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Scope: Treatment of adults with metastatic non-small-cell lung cancer (NSCLC)

### 5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 15.2.

### 5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See also Annex I 15.3.

#### 5.3.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/X/0089/G

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Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to:

- 1) Introduce a new pharmaceutical form (granules in single-dose container) associated with a new strength (0.15 mg).
- 2) Introduce a new pharmaceutical form (coated granules in sachet) associated with 3 new strengths (0.5 mg, 1.5 mg and 2 mg);

The above two line extensions are grouped with a type II - C.I.6.a variation:

Extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim analysis from Study CV185325; this is an open-label, multi-centre, randomised, active controlled trial to provide PK data and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children who require anticoagulation for a venous



thromboembolism; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPCs are updated. The package leaflet and Annex II are updated in accordance. Version 21.0 of the RMP has also been submitted

### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

CHMP is evaluating a type II variation for Eliquis, a centrally authorised product containing apixaban, to introduce new pharmaceutical forms along with an extension of indication to add treatment of VTE and prevention of VTE in a subset of the paediatric population. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

### **Summary of advice**

- The RMP for Eliquis (apixaban) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 21.0 is submitted.
- PRAC considered that the current RMP safety concerns remain unchanged; however, in relation to the concern of medication errors linked to the paediatric formulation, PRAC agreed that this should be included as an important potential risk in the summary of safety concerns in the PSUR and monitored in the upcoming PSURs accordingly. Regarding the pharmacovigilance plan, PRAC agreed that no change to the existing one is required. Concerning the proposed additional risk minimisation measure (prescriber's guide) for the risk of bleeding, PRAC recommended changes to the key elements and did not endorse the inclusion of the key elements 'paediatric formulations' and 'that all patients administered Eliquis and/or caregivers of paediatric patients administering Eliquis paediatric formulations should be counselled about the preparation and dosing of the Eliquis paediatric formulations'.

## **6. Periodic safety update reports (PSURs)**

### **6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only**

See also Annex I 16.1.

#### **6.1.1. Atezolizumab - TECENTRIQ (CAP) - PSUSA/00010644/202305**

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tecentriq, a centrally authorised medicine containing atezolizumab and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tecentriq (atezolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning regarding the risk of immune-related adverse reactions in patients with pre-existing autoimmune disease. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>12</sup>.
- In the next PSUR, the MAH should continue to monitor cases of myositis, severe myositis, cholangitis sclerosing, autoimmune cholangitis and immune-mediated cholangitis. Also, the MAH should provide review of lichen planus, lichen sclerosus and other lichen disorders cases based on data from all sources (including clinical trials, non-interventional studies, post-marketing reports and scientific literature), to provide a discussion the possible causality relation between atezolizumab and lichen disorder and the need for any potential amendment to the product information and/or the RMP.

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.

#### **6.1.2. Coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) - VIDPREVTYN BETA (CAP) - PSUSA/00011035/202305**

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Applicant: Sanofi Pasteur

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Vidprevtyn beta, a centrally authorised medicine containing coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant) and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vidprevtyn beta (coronavirus (COVID-19) vaccine (B.1.351 variant, prefusion Spike delta TM protein, recombinant)) in the approved indication(s) remains unchanged.

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<sup>12</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to add dizziness as an undesirable effect with a frequency 'rare'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>13</sup>.
- In the next PSUR, the MAH should provide a re-evaluation of all cases reporting 'allergic and anaphylactic reactions', as well as a detailed description on how the causal assessment between VidPrevtyl Beta and vaccination failure is performed.

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.

### 6.1.3. Delamanid - DELTYBA (CAP) - PSUSA/00010213/202304

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Deltyba, a centrally authorised medicine containing delamanid and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Deltyba (delamanid) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'paradoxical drug reaction' as a warning and as an undesirable effect with a frequency 'not known', and to add nightmare as an undesirable effect, along with specific information for the paediatric population. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSURs, the MAH should further monitor, report and assess all new cases of liver disorders with abnormal liver tests (especially transaminases) but also genuine liver disorders, occurring in the PHOENIX<sup>15</sup> trial.

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.

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<sup>13</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>14</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>15</sup> A Phase III, open-label, multicenter trial (242-201-00004) compares the efficacy and safety of 26 weeks use of delamanid (DLM) versus 26 weeks of isoniazide (INH) for preventing confirmed or probable active tuberculosis during 96 weeks of follow-up among high-risk household contacts (HHCs) of adults with multidrug-resistant tuberculosis

#### 6.1.4. Durvalumab - IMFINZI (CAP) - PSUSA/00010723/202304

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

##### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imfinzi, a centrally authorised medicine containing durvalumab and issued a recommendation on its marketing authorisation(s).

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imfinzi (durvalumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add uveitis and immune-mediated arthritis as warnings and as undesirable effects, as well as to include recommendations for treatment modifications following the occurrence of these adverse reactions. In addition, the product information should be updated to add a warning regarding patients with pre-existing autoimmune disease. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.
- In the next PSUR, the MAH should provide a review of cases of polymyalgia rheumatica, including data from clinical trials, post marketing and literature and discuss the mechanistic plausibility, as well as the need to update the product information if warranted.

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.

#### 6.1.5. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/202304

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

##### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

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<sup>16</sup> Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Truvada, a centrally authorised medicine containing emtricitabine/tenofovir disoproxil issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Truvada (emtricitabine/tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on bone effects and to add bone mineral density decreased as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>17</sup>.
- In the next PSURs, the MAH should continue to monitor cases related with lack of efficacy, and to provide details on these cases (including a breakdown of pre-exposure prophylaxis indication vs treatment indications). In addition, the MAH should continue to monitor cases of renal toxicity and of bone events due to proximal renal tubulopathy/loss of bone mineral density, including any significant new safety information and focusing on patients without clear risk factors, with particular attention to the pre-exposure prophylaxis indication.

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.

#### **6.1.6. Fenofibrate, pravastatin - PRAVAFENIX (CAP) - PSUSA/00001363/202304**

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Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Pravafenix, a centrally authorised medicine containing fenofibrate/pravastatin and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Pravafenix (fenofibrate/pravastatin) in the approved indication(s) remains unchanged.

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<sup>17</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- Nevertheless, the product information should be updated to add muscle rupture as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the MAH should continue to closely monitor the risks of off-label use and bullous pemphigoid, as well as the issue of pharmacogenetic effects regarding fenofibrate/pravastatin and provide an analysis based on all available sources, including MAH's databases, clinical trials, scientific literature and post-marketing data.

The frequency of PSUR submission should be revised from two-yearly to three-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

#### 6.1.7. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - PSUSA/00010868/202304

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Kaftrio, a centrally authorised medicine containing ivacaftor/tezacaftor/elexacaftor and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Kaftrio (ivacaftor/tezacaftor/elexacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on breastfeeding in order to reflect the current available data. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cases of acute pancreatitis, including data from literature and discuss whether an update of the product information is warranted. Additionally, the MAH should discuss on the increased reporting rate on the risk of susceptibility to influenza virus infection and whether amendments to the product information are warranted. Finally, the MAH should provide an updated cumulative review of cases of insomnia and fatigue, including cases of asthenia, hypersomnia or any relevant asthenic conditions.

<sup>18</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>19</sup> Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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.

#### 6.1.8. Meningococcal group A, C, W135, Y conjugate vaccine<sup>20</sup> - MENQUADFI (CAP); NIMENRIX (CAP) - PSUSA/00010044/202304

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Applicant: Sanofi Pasteur (MenQuadfi), Pfizer Europe MA EEIG (Nimenrix)

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

##### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Menquadfi, a centrally authorised medicine containing meningococcal group A, C, W135, Y conjugate vaccine (conjugated to tetanus toxoid carrier protein), and issued a recommendation on its marketing authorisation(s).

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Menquadfi (meningococcal group A, C, W135, Y conjugate vaccine, (conjugated to tetanus toxoid carrier protein)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a review of cases of febrile convulsions from clinical trials and post-marketing data.
- The MAH should submit to EMA, within 60 days, a cumulative review of cases of hypersensitivity/allergic reaction (including anaphylaxis) and discuss whether an update of the product information is warranted.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

#### 6.1.9. Parecoxib - DYNASTAT (CAP) - PSUSA/00002314/202303

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

##### **Background**

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<sup>20</sup> Conjugated to tetanus toxoid carrier protein



For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Dynastat, a centrally authorised medicine containing parecoxib and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Dynastat (parecoxib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on use during pregnancy, based on the PRAC advice for non-steroidal anti-inflammatory drugs (NSAID)-containing medicinal products (see [PRAC minutes July 2022](#)). The package leaflet is updated accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.

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.

### **6.1.10. Tenofovir disoproxil - VIREAD (CAP) - PSUSA/00002892/202303 (with RMP)**

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Viread, a centrally authorised medicine containing tenofovir disoproxil and issued a recommendation on its marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Viread (tenofovir disoproxil) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning on bone effects and to add bone mineral density decreased as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSURs, the MAH should continue to monitor and discuss cases of renal and bone toxicity, focusing on cases reported in patients without clear risk factors and

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<sup>21</sup> Update of SmPC section 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

<sup>22</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

discuss the need for an update of the product information. In addition, the MAH should continue to monitor pregnancy and lactation through routine pharmacovigilance and present any new findings from spontaneous reports, literature data and clinical studies.

- The MAH should submit to EMA, within 90 days, a cumulative review of cases of dental disorders and increased parathyroid hormone, and provide more details on the cases of congenital anomalies and discuss whether an update of the product information is warranted.

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.

#### 6.1.11. Tremelimumab - IMJUDO (CAP); TREMELIMUMAB ASTRAZENECA (CAP) - PSUSA/00011038/202304

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Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

##### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imjudo and Tremelimumab Astrezeneca, centrally authorised medicines containing tremelimumab and issued a recommendation on its marketing authorisation(s).

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Imjudo and Tremelimumab Astrezeneca (tremelimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add uveitis and immune-mediated arthritis as warnings and as undesirable effects, as well as to include recommendations for treatment modifications following the occurrence of these adverse reactions. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.

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.

## 6.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See also Annex I 16.2.

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<sup>23</sup> Update of SmPC sections 4.2 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

### 6.2.1. Tacrolimus<sup>24</sup> - PROTOPIC (CAP); NAP - PSUSA/00002840/202303

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Applicant: LEO Pharma A/S (Protopic), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### **Background**

Tacrolimus is a calcineurin inhibitor indicated, as topical formulation, for treatment of moderate to severe atopic dermatitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Protopic, (a) centrally authorised medicine(s) containing tacrolimus, and nationally authorised medicines containing tacrolimus and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tacrolimus-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the warning against the use of tacrolimus ointment in patients with a skin barrier, adding pyoderma gangrenosum to the list of conditions mentioned. Therefore, the current terms of the marketing authorisations should be varied<sup>25</sup>.
- In the next PSUR, the MAHs for tacrolimus-containing products should provide a review of adverse reactions reported in patients with skin barrier defects and discuss whether an update of the product information is warranted.
- The MAHs for generic tacrolimus-containing products should align their risk management plans with the one for the reference product.

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.

### **6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only**

See also Annex I 16.3.

#### 6.3.1. Aceclofenac (NAP) - PSUSA/00000022/202303

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **Background**

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<sup>24</sup> Topical formulation(s) only

<sup>25</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Aceclofenac is a non-steroid phenyl acetic acid derivative with anti-inflammatory and analgesic effects indicated for the treatment of acute and chronic treatment of various inflammatory and/or painful conditions, such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, as well as for the treatment of lumbago, odontalgia, primary dysmenorrhoea, scapulohumeral peri-arthritis and extra-articular rheumatism, pain and/or rheumatic disorders, in adult patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing aceclofenac and issued a recommendation on their marketing authorisation(s).

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of aceclofenac-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of topical formulations should be updated to add a contraindication on the use of topical aceclofenac in the third trimester of pregnancy and a warning about the risk of use in the first two trimesters, unless clearly necessary. If use during pregnancy is justified, the lowest possible dose for the shortest treatment duration should be applied. In addition, in case the product information already includes a similar or stricter advice on use in pregnancy, the similar or stricter advice remains valid and should remain. Moreover, if the product information contains statements indicating no teratogenic effects or no relevant systemic exposure, this text should be removed. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

### **6.3.2. Ciprofloxacin<sup>27</sup> (NAP) - PSUSA/00000775/202304**

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Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ciprofloxacin is an antibiotic belonging to the fluoroquinolones class, indicated for treatment of a variety of Gram-negative and Gram-positive bacterial infections – indications for fluoroquinolones have been restricted following the Article 31 referral procedure (see [Fluoroquinolone and quinolone antibiotics: PRAC recommends restrictions on use \(europa.eu\)](https://european-council.europa.eu/media/en/pressts/press_corner/2018/doc/fluoroquinolone_antibiotics_prac_recommends_restrictions_on_use_europa.eu.pdf))

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<sup>26</sup> Update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

<sup>27</sup> Systemic use only

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ciprofloxacin (for systemic use) and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ciprofloxacin-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should monitor if new data emerge on posology in patient subgroups and provide a review of any relevant data of this aspect from scientific literature. In addition, the MAHs should provide a review of cases of increased intracranial pressure disorder and discuss whether an update of the product information is warranted. The MAHs should also provide a cumulative review of cases of joint disorders in children <18 years of age.

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.

### **6.3.3. Clarithromycin (NAP) - PSUSA/00000788/202304**

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Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

#### **Background**

Clarithromycin is an antibiotic for systemic use belonging to the macrolide class of antibiotics, indicated for the treatment of infections due to susceptible organisms in adults and children over 6 months including lower and upper respiratory tract infections, skin and soft tissue infections, mycobacterial infections including treatment of mycobacterium avium complex in human immunodeficiency virus (HIV) infected patients. It is also used for treatment of odontogenic infections and for the eradication of *H. pylori* infection.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing clarithromycin and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of clarithromycin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication regarding concurrent use of ivabradine, to amend the warning and the interaction with the direct oral anticoagulant edoxaban, and to add drug-drug interactions between clarithromycin and hydroxychloroquine or chloroquine, and between clarithromycin and

systemic or inhaled corticosteroids. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.

- In the next PSUR, the MAHs should provide a review of cases of visual impairment and blurred vision, together with a discussion on the possible biological plausibility and on the need for an update of the product information if warranted. All MAHs for clarithromycin-containing products should provide a review of cases of drug-drug interaction between clarithromycin and metoclopramide, as well as provide a cumulative review of cases of erythema multiforme in association with clarithromycin use, and discuss the need for an update of the product information.

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.

#### 6.3.4. Cytarabine (NAP) - PSUSA/00000911/202303

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

##### **Background**

Cytarabine is a pyrimidine nucleoside analogue, an antimetabolite, anti-neoplastic drug indicated, in combination with other cytostatic substances, for induction of remission, consolidation and maintenance of remission of acute non-lymphatic leukaemia, induction of remission and consolidation of remission of acute lymphatic leukaemia, intrathecal prophylaxis and treatment of leukemic infiltrations of the central nervous system (CNS), treatment of Non-Hodgkin's Lymphoma (NHL) of intermediate and high malignancy in adulthood and in children. It is also indicated for patients with non-ALL (acute lymphocytic leukaemia) acute, chronic myeloid leukaemia, diffuse lymphoma, blast cell crisis, diffuse large b-cell lymphoma, leukaemia secondary, leukemic infiltration brain, leukaemia relapse, and solid tumour, subject to certain conditions.

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of cytarabine-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the innovator MAH for cytarabine-containing products should provide a thorough analysis of cases under MedDRA SMQ narrow 'severe cutaneous adverse reaction' and to provide a cumulative review on toxic erythema of chemotherapy (TEC) and discuss the need for an update of the product information. In addition, all MAHs should include PRES as an important potential risk to the list of safety concerns presented in the PSUR and should present a review of cases of PRES.

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<sup>28</sup> Update of SmPC sections 4.3 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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.

### 6.3.5. Fentanyl<sup>29</sup> (NAP) - PSUSA/00001370/202304

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Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### **Background**

Fentanyl is a phenylpiperidine opioid. It is indicated, as transdermal patches, in adults for the management of severe chronic pain that requires continuous long-term opioid administration and for long-term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy. It is also indicated, as solution for injection, in adults and paediatric patients as an opioid analgesic supplement in general or regional anaesthesia, as an anaesthetic premedication, for induction of anaesthesia, as an adjunct in maintenance of general and regional anaesthesia as well as an anaesthetic agent with oxygen in selected high-risk patients undergoing major surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fentanyl (transdermal patches, solution for injection) and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of fentanyl-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add dysphagia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>30</sup>.
- In the next PSUR, all MAHs should monitor cases of sphincter of Oddi dysfunction, spasms of sphincter of Oddi, and pancreatitis and discuss if an update of the product information is warranted based on the new findings. The MAHs for fentanyl transdermal patches should continue to monitor cases of dependence, abuse and overdose, and provide an assessment on whether new risk minimisation measures should be implemented.

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.

### 6.3.6. Gentamicin<sup>31</sup> (NAP) - PSUSA/00009159/202303

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Applicant(s): various

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<sup>29</sup> Transdermal patches, solution for injection

<sup>30</sup> Update of SmPC section XX. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

<sup>31</sup> Systemic use only



PRAC Lead: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

### **Background**

Gentamicin is a broad-spectrum antibiotic of the aminoglycoside group indicated for the treatment of bacterial infections caused by susceptible pathogens in adults and paediatric patients.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gentamicin (for systemic use) and issued a recommendation on their marketing authorisation(s).

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of gentamicin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>32</sup>.
- In the next PSUR, all MAHs for gentamicin-containing products for systemic use should provide a cumulative review of cases of drug reaction with eosinophilia and systemic symptoms (DRESS), including data from clinical trials, post-marketing and literature.

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.

## **6.3.7. Isotretinoin (NAP) - PSUSA/00010488/202305**

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

### **Background**

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin) indicated as oral formulation(s) for the treatment of severe forms of acne, i.e. nodular or conglobate acne, or acne at risk of permanent scarring. It is also indicated for the treatment of acne which has failed to respond to standard therapies with systemic antibiotics and topical therapy.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing isotretinoin and issued a recommendation on their marketing authorisation(s).

### **Summary of recommendation(s) and conclusions**

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<sup>32</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

- Based on the review of the data on safety and efficacy, the benefit-risk balance of isotretinoin-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs for isotretinoin-containing products should provide a cumulative review of cases of psychiatric disorders and discuss whether an update to the Patient card is warranted to minimise this risk. In addition, the MAHs should provide a cumulative review of cases of osteomyelitis, as well as a review of new cases of drug-induced liver injury, including a causality assessment and discuss whether an update of the product information is warranted. Finally, the MAHs should provide a cumulative review of cases of persistence of sexual disorders, including data from clinical trials, post-marketing, observational studies and literature and a separate review of new cases of sexual dysfunction (including orgasm abnormal), alongside with a discussion on the biological mechanism.

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.

### 6.3.8. Nortriptyline (NAP) - PSUSA/00002192/202303

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Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

#### **Background**

Nortriptyline is a tricyclic antidepressant indicated for the treatment of major depression and depressive states (i.e in schizophrenia) in adults and for the treatment of nocturnal enuresis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nortriptyline and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of nortriptyline-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hyponatraemia as an undesirable effect with a frequency 'not known' and to add Brugada syndrome (unmasking) as a warning and as an undesirable effect with a frequency 'not known'. In addition, the product information should be updated to add Brugada syndrome (unmasking) and Brugada ECG pattern as overdose symptoms. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.

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<sup>33</sup> Update of SmPC sections 4.4, 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

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.

### 6.3.9. Piroxicam (NAP) - PSUSA/00002438/202304

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **Background**

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID), indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing piroxicam and issued a recommendation on their marketing authorisation(s).

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of piroxicam-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information of topical formulations of piroxicam-containing products should be updated to add a contraindication on the use in the third trimester of pregnancy and a warning about the risk of use in the first two trimesters, unless clearly necessary. Moreover, if use during pregnancy is justified, the lowest possible dose for the shortest treatment duration should be applied. Moreover, if use during pregnancy is justified, the lowest possible dose for the shortest treatment duration should be applied. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>34</sup>.
- In the next PSUR, all MAHs for piroxicam-containing products should provide a cumulative review of acute generalised exanthematous pustulosis (AGEP), including data from clinical trials, post-marketing report and literature, including a discussion on the biological plausibility and on the need to update the product information. In addition, all MAHs should include and address 'use during pregnancy' as an important potential risk in the list of safety concerns of the PSUR. Additionally, MAHs are reminded to comply with the baseline summary of safety concerns as recommended by PRAC (i.e. following the innovator's MAH).

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.

### 6.3.10. Pravastatin (NAP) - PSUSA/00002500/202303

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Applicant(s): various

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<sup>34</sup> Update of SmPC sections 4.3 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

### **Background**

Pravastatin is a competitive inhibitor of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, indicated for the treatment of primary hypercholesterolemia or mixed dyslipidaemia and as primary and secondary prevention for cardiovascular events, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing pravastatin and issued a recommendation on their marketing authorisation(s).

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pravastatin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add muscle rupture as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>35</sup>.
- In the next PSUR, the MAH should provide a review of cases of bullous pemphigoid and of depression and suicide/self-injury, as well as closely monitor the issue of pharmacogenetic effects regarding fenofibrate/pravastatin and provide an analysis based on all available sources, including MAH's databases, clinical trials, scientific literature and post-marketing data including a discussion on the need to update the product information, as warranted.

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

#### **6.3.11. Racecadotril (NAP) - PSUSA/00002602/202303**

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Applicant(s): various

PRAC Lead: Mónica Martínez Redondo

Scope: Evaluation of a PSUSA procedure

### **Background**

Racecadotril is the prodrug of thiorphan, a selective and potent orally active enkephalinase inhibitor indicated for the symptomatic treatment of acute diarrhoea in adults, children and infants older than three months.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing racecadotril and issued a recommendation on their marketing authorisation(s).

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<sup>35</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of racecadotril-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with a frequency 'not known' and to add anaphylactic shock as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>36</sup>.

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

#### **6.3.12. Venlafaxine (NAP) - PSUSA/00003104/202305**

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Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **Background**

Venlafaxine is a dual-acting serotonin (5-HT) and norepinephrine reuptake inhibitor (SNRI), indicated for the treatment of depression, anxiety or generalised anxiety disorder (GAD), social anxiety disorder (SAD) and panic disorder (PD), as well as for the prevention of relapse and prevention of recurrence of depression.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing venlafaxine and issued a recommendation on their marketing authorisation(s).

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the benefit-risk balance of venlafaxine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add hypoglycaemia as a overdose symptom. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>37</sup>.

The frequency of PSUR submission should be revised from yearly to five-yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

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<sup>36</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

<sup>37</sup> Update of SmPC section 4.9. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

## 6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

## 6.5. Variation procedure(s) resulting from PSUSA evaluation

None

## 6.6. Expedited summary safety reviews<sup>38</sup>

None

# 7. Post-authorisation safety studies (PASS)

## 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>39</sup>

See Annex I 17.1.

## 7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>40</sup>

See Annex I 17.2.

## 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>41</sup>

See also Annex I 17.3.

### 7.3.1. Valproate<sup>42</sup> (NAP) - EMEA/H/N/PSR/J/0043

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Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Final study report for a retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring

#### Background

Sodium valproate is indicated for the treatment of epilepsy and manic episodes when lithium is contraindicated or not tolerated. Valproate is also indicated in the prophylaxis of migraine attacks in some EU Member States.

Further to the conclusions dated 2018 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1454](#)) conducted by PRAC for valproate-containing medicines, the MAHs were required as a condition to the marketing authorisation(s) ([Annex IV](#)) to conduct a retrospective observational study to investigate the association between paternal

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<sup>38</sup> Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

<sup>39</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>40</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

<sup>41</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>42</sup> Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium

exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring. The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to the EMA the final results of the study. For further background, see [PRAC minutes May 2023](#), [PRAC minutes June 2023](#), [PRAC minutes July 2023](#), [PRAC minutes October 2023](#)<sup>43</sup> and [PRAC minutes November 2023](#)<sup>44</sup>.

#### **Summary of recommendation(s) and conclusions**

- PRAC was informed about the feedback from a stakeholder meeting held on 16 November 2023.
- At the organisational, regulatory and methodological matters (ORGAM) meeting held on 14 December 2023, PRAC was informed about the feedback from the Scientific Advisory Group on Neurology (SAG-N, enriched with psychiatry expertise) meeting held on 04 December 2023.

### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>45</sup>**

See also Annex I 17.4.

#### **7.4.1. Hepatitis B surface antigen (rDNA) - HEPLISAV B (CAP) - EMEA/H/C/005063/II/0031**

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Applicant: Dynavax GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from study DV2-HBV-28 - Post-marketing observational surveillance study to evaluate pregnancy outcomes among women who receive HEPLISAV-B or Engerix-B; HBV-28 was conducted using the same patient population as two observational post-marketing surveillance studies designed to evaluate the incidence of AMI (HBV-25) or new-onset immune-mediated diseases, herpes zoster, and anaphylaxis (HBV-26) in recipients of HEPLISAV-B compared with recipients of Engerix-B. The primary objective of this study was to describe and compare pregnancy outcomes in recipients of HEPLISAV-B and recipients of Engerix-B. The package leaflet is updated accordingly. The RMP version 1.4 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

#### **Background**

For background information on substance(s) and indication(s) of centrally authorised product(s) identified as 'CAP', see [Human medicine European public assessment report \(EPAR\)](#) on the EMA website.

The MAH conducted a non-imposed non-interventional PASS to evaluate pregnancy outcomes among women who receive HEPLISAV-B or Engerix-B and submitted the final report of the study. The Rapporteur assessed the MAH's final study report.

#### **Summary of advice**

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<sup>43</sup> Held 25-28 September 2023

<sup>44</sup> Held 23-26 October 2023

<sup>45</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be considered acceptable provided that the MAH submits satisfactory responses to a RSI.
- In view of the limited data, PRAC considered that an update of the product information is not warranted at this stage. The MAH should submit further information related to the data analysis and interpretation of the study results. In addition, the MAH should discuss whether the 'safety in pregnancy and lactation' should remain as missing information in the summary of safety concerns in the RMP. PRAC agreed that the use in pregnant or breast-feeding women should be continued to be monitored via routine pharmacovigilance.

## **7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation**

See Annex I 17.5.

## **7.6. Others**

None

## **7.7. New Scientific Advice**

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

## **7.8. Ongoing Scientific Advice**

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

## **7.9. Final Scientific Advice (Reports and Scientific Advice letters)**

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

# **8. Renewals of the marketing authorisation, conditional renewal and annual reassessments**

## **8.1. Annual reassessments of the marketing authorisation**

See Annex I 18.1.

## **8.2. Conditional renewals of the marketing authorisation**

See Annex I 18.2.

## **8.3. Renewals of the marketing authorisation**

See Annex I 18.3.



## **9. Product related pharmacovigilance inspections**

### **9.1. List of planned pharmacovigilance inspections**

None

### **9.2. Ongoing or concluded pharmacovigilance inspections**

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the minutes.

### **9.3. Others**

None

## **10. Other safety issues for discussion requested by CHMP or EMA**

### **10.1. Safety related variations of the marketing authorisation**

None

### **10.2. Timing and message content in relation to Member States' safety announcements**

None

### **10.3. Other requests**

None

### **10.4. Scientific Advice**

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

## **11. Other safety issues for discussion requested by the Member States**

### **11.1. Safety related variations of the marketing authorisation**

None

### **11.2. Other requests**

None

## **12. Organisational, regulatory and methodological matters**

### **12.1. Mandate and organisation of PRAC**

#### **12.1.1. PRAC membership**

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The Chair welcomed Petar Mas as the new alternate for Croatia and Carla Torre as the new alternate for Portugal.

#### **12.1.2. Vote by proxy**

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Annalisa Capuano gave a proxy to Amelia Cupelli to vote on behalf of during the entire meeting.

#### **12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q3 2023**

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In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA Secretariat updated PRAC on the quantitative measures collected for Q3 2023 of PRAC meetings. For previous update, see [PRAC minutes September 2023](#)<sup>46</sup>.

### **12.2. Coordination with EMA Scientific Committees or CMDh-v**

None

### **12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups**

None

### **12.4. Cooperation within the EU regulatory network**

#### **12.4.1. Health threats and EMA Emergency Task Force (ETF) activities - update**

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The EMA Secretariat provided PRAC with an update on the characteristics of the post-COVID-19 condition and post-acute sequelae of COVID-19, including the risk factors and on the new SARS-CoV-2 variants. An update was provided also on various outbreaks around the world such as swine flu, bird flu, as well as on the development of new influenza vaccines.

### **12.5. Cooperation with International Regulators**

None

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<sup>46</sup> Held 28-31 August 2023

## **12.6. Contacts of PRAC with external parties and interaction with the Interested Parties to the Committee**

None

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2024**

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PRAC lead: Sabine Straus, Martin Huber

The EMA Secretariat provided an overview of planned topics to be included in the PRAC work plan 2024 which is scheduled to be adopted in January 2024.

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q3 2023 and predictions**

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 December 2023, the EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes September 2023](#).

### **12.8.2. PRAC workload statistics – Q3 2023**

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 December 2023, the EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q3 2023, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes September 2023](#).

## **12.9. Pharmacovigilance audits and inspections**

### **12.9.1. Pharmacovigilance systems and their quality systems**

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

## **12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list**

### **12.10.1. Periodic safety update reports**

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None

### **12.10.2. Granularity and Periodicity Advisory Group (GPAG)**

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PRAC lead: Menno van der Elst

EMA Secretariat provided to PRAC an update on the work of the GPAG and launched a call for nomination of a new GPAG Chair, as well as of additional members to the group. The members should send their interest in writing .

### **12.10.3. PSURs repository**

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None

### **12.10.4. Union reference date list – consultation on the draft list**

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PRAC endorsed the draft revised EURD list, version December 2023, reflecting PRAC’s comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of December 2023, the updated EURD list was adopted by CHMP and CMDh at their December 2023 meetings and published on the EMA website, see: [Home> Human Regulatory>Post-authorisation>Pharmacovigilance>Periodic safety update reports>> List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

## **12.11. Signal management**

### **12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group**

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PRAC lead: Menno van der Elst

PRAC was updated on the ongoing activities and the progress from the SMART working group – work stream Methods meeting held on 09 October 2023, such as discussions related to pharmacoepidemiological considerations for O/E analysis for vaccines using spontaneous reports, masking effect on signal detection and regulatory decision-making, as well as an overview of the activities performed so far in finalising and implementing the pregnancy algorithm in EudraVigilance. PRAC noted the information.

## **12.12. Adverse drug reactions reporting and additional monitoring**

### **12.12.1. Management and reporting of adverse reactions to medicinal products**

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None

### **12.12.2. Additional monitoring**

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None

### **12.12.3. List of products under additional monitoring – consultation on the draft list**

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PRAC was informed on the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on the EMA website, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

## **12.13. EudraVigilance database**

### **12.13.1. Activities related to the confirmation of full functionality**

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None

## **12.14. Risk management plans and effectiveness of risk minimisations**

### **12.14.1. Risk management systems**

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None

### **12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations**

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None

## **12.15. Post-authorisation safety studies (PASS)**

### **12.15.1. Post-authorisation Safety Studies – imposed PASS**

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None

### **12.15.2. Post-authorisation Safety Studies – non-imposed PASS**

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None

## **12.16. Community procedures**

### **12.16.1. Referral procedures for safety reasons**

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None

### 12.16.2. Referral procedures - minor revision to the (Co-)Rapporteur assessment report templates

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 December 2023, the EMA Secretariat informed PRAC about a revision of the (Co)-Rapporteur assessment report template for the referral procedures to include an annex to reflect the changes recommended to the risk management plan. PRAC noted the information.

## 12.17. Renewals, conditional renewals, annual reassessments

None

## 12.18. Risk communication and transparency

### 12.18.1. Public participation in pharmacovigilance

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None

### 12.18.2. Safety communication

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None

## 12.19. Continuous pharmacovigilance

### 12.19.1. Incident management

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None

## 12.20. Impact of pharmacovigilance activities

### 12.20.1. Implementation of EU risk minimisation measures for medicinal products in clinical guidelines (SC01/EMA/2020/46/TDA/L4.02) - PRAC Sponsor's critical appraisal

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PRAC lead: Martin Huber

PRAC discussed the results of the study 'Implementation of EU risk minimisation measures (RMM) for medicinal products in clinical guidelines' ([EUPAS47588](#)) commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities. The study showed great variability in the number of actors issuing guidelines and number of issued guidelines for selected therapeutic area per country, as well as a rather low implementation rate of RMM in guidelines. PRAC concluded that the qualitative study provided very useful insights into the interplay between RMMs and guidelines and that there is no need for further regulatory measures to follow-up on the matter.

## 12.21. Others

### 12.21.1. EMA-HMA catalogues of real-world data sources and non-interventional studies

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The EMA Secretariat presented to PRAC an update on the development of the EMA-HMA catalogues of real-world data sources and non-interventional studies following the Priority

Recommendations developed by the Big Data Steering Group recommendations to promote data discoverability through the identification of metadata and to advance the use of big data in the European regulatory network. The catalogues will go live in 2024. PRAC noted the information.

#### 12.21.2. [Q&A on 'What is the day zero for ICSRs described in physical/hard copy local journals?' published in January 2023 - proposal for update](#)

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At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 December 2023, the EMA Secretariat presented to PRAC a proposal to update the question related to determination of day zero for ICSRs described in physical/hard copy local journals and published in the **[Q&A version published in January 2023](#)**. The proposal was presented after consultation with several groups, including EudraVigilance Expert Working Group (EV-EWG), Pharmacovigilance Inspectors Working Group (PhV IWG) and Pharmacovigilance Business Team. PRAC members were invited to send their comments in writing by 19 January 2023.

#### 12.21.3. [Real World Evidence and Data analysis and real-world interrogation network \(DARWIN EU®\) - quarterly update](#)

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PRAC lead: Sabine Straus, Nathalie Gault, Maria Martinez Gonzalez, Liana Gross-Martirosyan

The EMA Secretariat presented to PRAC the regular progress update on the establishment of the DARWIN EU® Coordination Centre, including the status of the initiated studies, information about the data partners, the process for proactively identification of research questions, as well as on the pilot project aiming to conduct studies leveraging genetic data linked to real-world data sources. Finally, PRAC was informed about the upcoming events on RWD: [HMA/EMA Big Data Stakeholder Forum](#) and the [Multistakeholder workshop on Patient Registries](#).

#### 12.21.4. [Real World Evidence and Data analysis and real-world interrogation network \(DARWIN EU®\) - results of a drug utilization study of prescription opioids](#)

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PRAC lead(s): Sabine Straus, Nathalie Gault, Liana Gross-Martirosyan

At the organisational, regulatory and methodological matters (ORGAM) meeting on 14 December 2023, the EMA secretariat presented to PRAC the results of a drug utilisation study of prescription opioids commissioned by EMA to investigate the incidence and prevalence of use of opioids during the study period 2012-2022 and to determine the duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing. The study report will be published on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) - [EUPAS105641 \(encepp.eu\)](#).

#### 12.21.5. [Stakeholder engagement for risk minimisation - PRAC Risk Minimisation Alliance \(PRISMA\) - pilot report for 2022-2023 and planning for 2024](#)

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PRAC lead(s): Liana Gross-Martirosyan

The EMA Secretariat presented to PRAC an update on the PRISMA pilot and its role, as well as the steps towards a more operative way of working. PRAC has taken note of the proposed actions and activities for PRISMA to focus on next year. These actions are primarily related to the integration of risk minimisation measures (RMMs) in the healthcare systems, including discussions around the role of prescribing and dispensing software for enhancing RMMs' awareness and implementation, as well as on the possibility of collecting RMMs at the level of EU and making them publicly available in a central repository. PRAC welcomed the information and highlighted the importance of healthcare professionals and patients input in decision-making process.

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>47</sup>

As per the agreed criteria for new signal(s), PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>48</sup>.

### 14.1. New signals detected from EU spontaneous reporting systems

#### 14.1.1. Brolucizumab – BEOVU (CAP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Signal of scleritis

EPITT 20016 – New signal

Lead Member State(s): DE

#### 14.1.2. Doxycycline (NAP)

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Applicant: various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of suicidality

EPITT 19997 – New signal

Lead Member State(s): NL

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<sup>47</sup> Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

<sup>48</sup> Either MAH(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting



### 14.1.3. Ethambutol (NAP)

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Applicant: various

PRAC Rapporteur: Sonja Hrabcik

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 20018 – New signal

Lead Member State(s): AT

### 14.1.4. Glatiramer (NAP)

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Applicant: various

PRAC Rapporteur: Karin Erneholm

Scope: Signal of anaphylaxis with a long latency

EPITT 19990 – New signal

Lead Member State(s): DK

## 14.2. New signals detected from other sources

### 14.2.1. Afatinib - GIOTRIF (CAP)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of growth of eyelashes

EPITT 19987 – New signal

Lead Member State(s): SE

## 15. Annex I – Risk management plans

### 15.1. Medicines in the pre-authorisation phase

As per the agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the medicine(s) mentioned below under evaluation for initial marketing authorisation application. Information on the medicines containing the active substance(s) listed below will be made available following the CHMP opinion on their marketing authorisation(s).

#### 15.1.1. Apremilast - EMEA/H/C/006208

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Scope: treatment of psoriatic arthritis, psoriasis, Behçet's disease

#### 15.1.2. Buprenorphine - EMEA/H/C/006188

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Scope: treatment of opioid drug dependence

### 15.1.3. Nintedanib - EMEA/H/C/006179

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Scope: treatment of idiopathic pulmonary fibrosis (IPF), chronic fibrosing interstitial lung diseases (ILDs) and lung diseases (ILDs) systemic sclerosis associated interstitial lung disease (SSc-ILD)

### 15.1.4. Ustekinumab - EMEA/H/C/006183

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Scope: treatment of Crohn's disease and Ulcerative colitis, treatment of Crohn's disease, Ulcerative colitis, Plaque psoriasis, Paediatric plaque psoriasis and Psoriatic arthritis (PsA)

## 15.2. Medicines in the post-authorisation phase – PRAC-led procedures

As per the agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the medicine(s) mentioned below.

### 15.2.1. Aflibercept - ZALTRAP (CAP) - EMEA/H/C/002532/II/0071

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Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP version 5.0 in order to update the Risk Minimization Measures and List of Safety Concerns removing "Nephrotic syndrome", "Cardiac failure and ejection fraction decreased", "Posterior reversible encephalopathy syndrome", "Thrombotic microangiopathy" and "Osteonecrosis of jaw" of the important identified risks, "Reproductive and developmental toxicity" as an important potential risk and "Safety in patients with severe hepatic impairment" of the missing information, following the assessment of PSUSA/00010019/202108

### 15.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0043

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of an updated RMP version 22.1 in order to remove existing additional pharmacovigilance activities (category 3 studies): Study I4V-MC-JAJA (JAJA) and Study I4V-MC-JAJD (JAJD)

### 15.2.3. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/000709/II/0090

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 18.0 in order to reflect the proposed revised commitments to assess the growth and development disorders and bone mineral metabolism disorders in paediatric subjects

#### 15.2.4. Doxorubicin - CAELYX PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/000089/II/0107

Applicant: Baxter Holding B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP version 6.1 in order to align to GVP Module V Revision 2 requirements, following a request received within the Assessment Report for procedure EMEA/H/C/PSUSA/00001172/202111

#### 15.2.5. Ivabradine - CORLENTOR (CAP) - EMEA/H/C/000598/WS2569/0059; IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/WS2569/0019; PROCORALAN (CAP) - EMEA/H/C/000597/WS2569/0058

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope: C.I.11.z - To update the RMP to delete the obsolete products (Ivabradine Egis and Ivabradine Proterapia) that are still mentioned in the RMP

#### 15.2.6. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0127

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: David Olsen

Scope: Submission of an updated RMP version 9.0 in order to remove the important potential risks 'Change in meningococcal epidemiology/serogroup replacement' and 'Lack of Efficacy' from the list of the safety concerns, to remove 'Long-term persistence of the vaccine response and need for a booster dose' as missing information and to remove 'Use during pregnancy' from the list of safety concerns

#### 15.2.7. Sildenafil - REVATIO (CAP) - EMEA/H/C/000638/II/0107

Applicant: Upjohn EESV

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 8.0 in order to remove "Long-term Mortality" as missing information based on the completion of Study A1481324 - A multinational, multicentre study to assess the effects of oral sildenafil on mortality in adults with pulmonary arterial hypertension (PAH). In addition, the MAH took the opportunity to reflect the completion of the Studies A1481324 and A1481319

#### 15.2.8. Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/II/0047

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Submission of an updated RMP version 10.1 in order to remove all important potential risks and missing information from the list of safety concerns, to align with the new RMP format according to Good Pharmacovigilance Practices Module V Revision 2 and to remove one closed PASS of category 2 (Recordati Rare Diseases's Vedrop registry) from the

pharmacovigilance plan

### **15.3. Medicines in the post-authorisation phase – CHMP-led procedures**

As per the agreed criteria, PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the medicine(s) mentioned below.

#### **15.3.1. Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/II/0010**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include treatment of adolescents 12 to < 18 years of age with moderate to severe atopic dermatitis for CIBINQO based on final results from non-clinical study 00655292 [21GR211] and interim results from clinical study B7451015; this is a Phase III multi-center, long-term extension study investigating the efficacy and safety of abrocitinib, with or without topical medications, administered to subjects aged 12 years and older with moderate to severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

#### **15.3.2. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/II/0044, Orphan**

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Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Extension of indication for the prevention of phototoxicity in adolescent patients (12 to under 18 years of age) with erythropoietic protoporphyria (EPP), based on the analysis of the safety and efficacy data available. As a consequence, sections 4.1, 4.2 and 4.4 of the SmPC are updated. The package leaflet is updated in accordance. Version 9.4 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce a minor editorial correction to the product information

#### **15.3.3. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/II/0051**

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Applicant: Les Laboratoires Servier

PRAC Rapporteur: Pernille Harg

Scope: Extension of indication to include new therapeutic indication in adolescents aged 12 to 17 years for the treatment of moderate to severe major depressive episodes, if depression is unresponsive to psychological therapy alone, for Valdoxan, further to the results of the phase 2 (CL2-20098-075) and phase 3 (CL3-20098-076) paediatric clinical studies included in the Paediatric Investigation Plan number EMEA-001181-PIP-11; as a consequence the sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly. The updated RMP version 25.1 has also been submitted.

#### **15.3.4. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/WS2467/0051; FOSAVANCE (CAP) -**

Applicant: Organon N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Update of sections 4.4 and 4.8 the SmPC in order to include information on the risk of low-energy fractures in bones other than femur based on post-marketing case reports and the literature. The package leaflet and Labelling are updated accordingly. In addition, the MAH the opportunity to update the list of local representatives in the package leaflet, to bring the product information in line with the latest QRD template and to introduce editorial changes. A justification for not submitting the RMP was provided

#### 15.3.5. [Alpelisib - PIQRAY \(CAP\) - EMA/H/C/004804/II/0022/G](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application comprising two type II variations (C.I.4) as follows:

- Update of sections 4.2, 4.4, 4.8 of the SmPC in order to update information on prophylactic use of metformin for hyperglycaemia based on the results from study CBYL719CES01T (METALLICA). METALLICA is a Phase II study aimed to evaluate the effect of prophylactic use of metformin for hyperglycaemia in HR-positive, HER2-negative, PIK3CA-mutated advanced breast cancer patients treated with alpelisib plus endocrine therapy.
- Update of section 4.8 of the SmPC in order to add "uveitis" to the list of adverse drug reactions (ADRs) with frequency "Not known" based on a cumulative review of the MAH safety database and literature.

The package leaflet and Annex II are updated accordingly. The RMP version 7.0 has also been submitted

#### 15.3.6. [Atezolizumab - TECENTRIQ \(CAP\) - EMA/H/C/004143/II/0081](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include, in combination with bevacizumab, adjuvant treatment of adult patients with hepatocellular carcinoma (HCC) at high risk of recurrence after surgical resection or ablation for TECENTRIQ, based on final results from study WO41535 (IMbrave050); this is a phase III, randomised, multi-centre, international, open-label study, conducted to evaluate the efficacy and safety of adjuvant therapy of atezolizumab in combination with bevacizumab in patients with completely resected or ablated HCC who were at high risk for disease recurrence. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 28.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes

#### 15.3.7. [Atezolizumab - TECENTRIQ \(CAP\) - EMA/H/C/004143/II/0082](#)

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include first-line treatment of adult patients with non-small cell lung cancer (NSCLC) who are ineligible for platinum-based chemotherapy and who do not have EGFR mutant or ALK-positive disease, who have: locally advanced unresectable NSCLC not amenable for definitive chemoradiotherapy, or metastatic NSCLC, for TECENTRIQ, based on final results from study MO29872 (IPSOS); this is a phase 3, open-label, multicenter, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment naive advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) non-small cell lung cancer who are deemed unsuitable for platinum-containing therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. Version 29.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

### 15.3.8. Bezlotoxumab - ZINPLAVA (CAP) - EMEA/H/C/004136/II/0037

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include treatment of the paediatric population (1 to 18 years of age) for ZINPLAVA, based on final results from study MK-6072-001 (MODIFY III) listed as a category 3 study in the RMP; this is a phase 3, randomised, placebo-controlled, parallel-group, multi-site, double-blind trial evaluating the safety, tolerability, pharmacokinetics (PK) and efficacy of a single infusion of bezlotoxumab in paediatric participants from 1 to <18 years of age receiving antibacterial drug treatment for Clostridioides difficile infection (CDI). 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. Version 2.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

### 15.3.9. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/II/0035/G, Orphan

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Grouped variation consisting of: 1) Addition of prefilled syringe presentation for the 10 mg strength; addition of prefilled syringe presentation for the 20 mg strength; addition of prefilled syringe presentation for the 30 mg strength; 2) other quality variations

### 15.3.10. Ciltacabtagene autoleucl - CARVYKTI (CAP) - EMEA/H/C/005095/II/0021, Orphan

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a product information, have demonstrated disease progression on or after the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing,

Phase 3, randomised, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the product information. As part of the application the MAH is requesting a 1-year extension of the market protection

#### 15.3.11. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0027

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of sections 4.5 and 4.6 of the SmPC in order to add information regarding the use of Mavenclad with oral contraceptives based on the final study results from the drug-drug interaction study (MS 700568-0031). This is a randomised, double-blind, 2-period, 2-sequence, crossover Phase I study with a 1-month run-in period to examine the effect of cladribine tablets on the pharmacokinetics of a monophasic oral contraceptive containing ethinyl estradiol and levonorgestrel (microgynon) in pre-menopausal women with Relapsing Multiple Sclerosis (RMS). The Annex II and package leaflet are updated accordingly. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity implement editorial changes to sections 4.2 and 4.4 of the SmPC

#### 15.3.12. Defatted powder of *Arachis hypogaea* L., semen (peanuts) - PALFORZIA (CAP) - EMEA/H/C/004917/II/0014/G

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Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variation consisting of:

C.I.6.a (Extension of indication): Extension of indication to include treatment of patients 1 to 3 years old for PALFORZIA, based on final results from study ARC005; this is a Phase 3 randomised, double-blind, placebo-controlled Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON) to evaluate the safety and efficacy of peanut powder in terms of superiority of placebo in children of 1 year to less than 4 years of age with peanut allergy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.5 and 8 of the SmPC are updated. The package leaflet and Labelling were updated accordingly. Version 1.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to update the list of local representatives in the package leaflet. As part of the application the MAH is requesting a 1-year extension of the market protection.

B.II.e.5.a: Introduction of a new pack-size of 16 capsules of 1 mg (Level 0) in blisters for PALFORZIA, 1 mg, oral powder in capsules for opening.

#### 15.3.13. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0063

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication to include treatment of adult men with high-risk biochemical

recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy, for Xtandi, based on final results from study MDV3100-13 (EMBARC); this is a phase 3, randomised, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in men with high-risk non-metastatic prostate cancer progressing after definitive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 18.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information and to update the list of local representatives in the package leaflet

#### **15.3.14. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58<sup>49</sup>) - EMEA/H/W/002320/II/0016**

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Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Extension of indication to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense* for FEXINIDAZOLE WINTHROP based final results from study DNDI-FEX-07-HAT - Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial; this is a phase-II/III, multicenter, open-label, non-randomised, single-arm clinical trial to assess the efficacy and safety of fexinidazole in patients with r-HAT. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted

#### **15.3.15. Human fibrinogen, human thrombin - VERASEAL (CAP) - EMEA/H/C/004446/II/0027**

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Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of children for VeraSeal, based on final results from study IG1405; this is a prospective, randomised, active-controlled, single-blind, parallel group clinical trial to evaluate the safety and efficacy of VeraSeal as an adjunct to haemostasis during surgery in paediatric subjects. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted

#### **15.3.16. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0087**

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Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults for HyQvia, based on final results from studies 161403 and ABV-771-1001; and interim results from study 161505. 161403 and 161505 are interventional Phase III efficacy and safety studies respectively, while ABV-771-1001 is an

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<sup>49</sup> Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)



interventional Phase I safety study. 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 labelling are updated in accordance. Version 14.0 of the RMP has also been submitted

#### **15.3.17. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0038, Orphan**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to modify the warning on liver monitoring and drug-induced liver injury and to add 'drug-induced liver injury' to the list of adverse drug reactions (ADRs) with frequency 'not known', following the request in the assessment report for PAM procedure EMEA/H/C/004782/LEG/008. The Annex II and package leaflet are updated accordingly. The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor updates to the product information

#### **15.3.18. Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0026, Orphan**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086). Study WI203581 is a Phase 1/2, multicenter, European, multi-cohort, open-label study in pediatric patients ( $\geq 1$  and  $< 18$  years of age) with R/R CD22-positive Acute Lymphoblastic Leukemia (ALL); and study WI235086 is an open-label, multicenter Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive ALL. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted

#### **15.3.19. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0039, Orphan**

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Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC based on interim results from study VX19-445-107 (Study 107) listed as a category 3 study in the RMP; this is a Phase III, open-label study evaluating the long-term safety and efficacy of VX445/TEZ/IVA combination therapy in subjects with cystic fibrosis who 6 years of age and older. The RMP version 7.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes in the SmPC

#### **15.3.20. Maralixibat - LIVMARLI (CAP) - EMEA/H/C/005857/II/0003/G, Orphan**

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Applicant: Mirum Pharmaceuticals International B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variation consisting of: 1) Extension of indication to include treatment of

Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 2 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomised, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. 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 and Annex II are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes; 2) B.I.b.1.b

#### 15.3.21. Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/II/0017/G, Orphan

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped application comprising two type II variations (C.I.4) as follows:

- Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study LINC4 (study CLCI699C2302 - A Phase III, multi-center, randomised, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease).

- Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study LINC3 (study CLCI699C2301 - A Phase III, multi-center, double-blind, randomised withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease).

The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to introduce some minor editorial changes to the product information

#### 15.3.22. Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0053

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, based on final results from study FLAURA2 (D5169C00001); this is a Phase III, open-label, randomised study of osimertinib with or without platinum plus pemetrexed chemotherapy, multicentre study to assess the efficacy and safety of TAGRISSO as first-line treatment in patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 16 of the RMP has also been submitted

#### 15.3.23. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0017

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to include information regarding moderate and severe hepatic impairment based on final results from study GP43163 listed as a category 3 study in the RMP; this is a Phase I, open-label, single-dose study to evaluate the pharmacokinetics and safety of pralsetinib in subjects with moderate or severe hepatic impairment compared to healthy subjects. The RMP version 1.8 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to update the marketing authorisation renewal date in Annex I

#### **15.3.24. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0045**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Extension of indication to include the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, Stage II or Stage III early breast cancer, irrespective of nodal status, in combination with an aromatase inhibitor (AI) for Kisqali based on study CLEE011O12301C (NATALEE); this is a global, Phase III, multicenter, randomised, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy (ET) versus ET alone as adjuvant treatment in patients with HR-positive, HER2-negative, early breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

#### **15.3.25. Rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/X/0042/G**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) Extension application to introduce a new pharmaceutical form associated with new strength (2.5 mg dispersible tablets). The new presentation is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in patients  $\geq 2$  to  $<18$  years of age and weighing at least 10 kg to less than 25 kg. The product information and RMP have been updated in accordance. 2) Type II variation (C.I.6.a) to modify the approved therapeutic indication of the already authorised 25 mg film-coated tablets presentation to include, in combination with other antiretroviral medicinal products, treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve and virologically suppressed (HIV-1 RNA less than 50 copies per ml) paediatric patients from 2 to less than 12 years weighing at least 25 kg, based on final results from study studies TMC278-TiDP38-C213 Cohort 2. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. The updated RMP version 10.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to Annex II and to update the list of local representatives in the package leaflet

### 15.3.26. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/II/0010/G

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Update of sections 4.2, 4.4, 4.8, 5.2 and 5.3 of the SmPC in order to change in the recommended dose and to update safety and efficacy information based on results from study 20190009 (CodeBreak 200) listed as a specific obligation in the Annex II, in order to fulfil SOB/001; and results from study 20170543 (CodeBreak 100) phase 2 part B. Study 20190009 is a phase 3 multicentre, randomised, open-label, active-controlled study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic non-small cell lung cancer (NSCLC) subjects with mutated KRAS p.G12C; while study 20170543 is a phase 1/2, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of AMG 510 monotherapy in subjects with advanced solid tumours with KRAS p.G12C mutation and AMG 510 combination therapy in subjects with advanced NSCLC with KRAS p.G12C mutation. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to update Annex II of the SmPC

### 15.3.27. Teriflunomide - TERIFLUNOMIDE ACCORD (CAP) - EMEA/H/C/005960/X/0002

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new strength of 7 mg film-coated tablets. The bioequivalence study data were submitted

### 15.3.28. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0063

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Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.2 of the SmPC in order to add information to support at-home self-administration of VPRIV by a trained patient and/or a caregiver based on post-marketing data and literature. The package leaflet and Annex IID are updated accordingly. The updated RMP version 13.0 has also been submitted

## 16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, PRAC concluded that the benefit-risk balance of the medicine(s) mentioned below remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per the agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs 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, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

## **16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only**

### **16.1.1. Abaloparatide - ELADYNOS (CAP) - PSUSA/00011029/202304**

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Applicant: Theramex Ireland Limited

PRAC Rapporteur: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

### **16.1.2. Alogliptin; alogliptin, metformin; alogliptin, pioglitazone - INCRESYNC (CAP); VIPDOMET (CAP); VIPIDIA (CAP) - PSUSA/00010061/202304**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.1.3. Andexanet alfa - ONDEXXYA (CAP) - PSUSA/00010764/202304**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.1.4. Asciminib - SCEMBLIX (CAP) - PSUSA/00011008/202304**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

### **16.1.5. Brigatinib - ALUNBRIG (CAP) - PSUSA/00010728/202304**

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

### **16.1.6. Bupivacaine<sup>50</sup> - EXPAREL LIPOSOMAL (CAP) - PSUSA/00010889/202304**

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Applicant: Pacira Ireland Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

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<sup>50</sup> Liposomal formulation(s) only

16.1.7. [Canagliflozin; canagliflozin, metformin - INVOKANA \(CAP\); VOKANAMET \(CAP\) - PSUSA/00010077/202303 \(with RMP\)](#)

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.8. [Capmatinib - TABRECTA \(CAP\) - PSUSA/00011022/202305](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Carla Torre

Scope: Evaluation of a PSUSA procedure

16.1.9. [Cholera vaccine \(inactivated, oral\) - DUKORAL \(CAP\) - PSUSA/00000730/202304](#)

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Applicant: Valneva Sweden AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.10. [Cobicistat, elvitegravir, emtricitabine, tenofovir alafenamide - GENVOYA \(CAP\) - PSUSA/00010449/202305](#)

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.11. [Conestat alfa - RUCONEST \(CAP\) - PSUSA/00000873/202304](#)

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Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.12. [Dimethyl fumarate, diroximel fumarate<sup>51</sup> - TECFIDERA \(CAP\); VUMERITY \(CAP\) - PSUSA/00010143/202303](#)

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.13. [Dolutegravir, rilpivirine - JULUCA \(CAP\) - PSUSA/00010689/202305](#)

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

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<sup>51</sup> Multiple sclerosis indication only

Scope: Evaluation of a PSUSA procedure

**16.1.14. Dostarlimab - JEMPERLI (CAP) - PSUSA/00010931/202304**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.15. Drospirenone, estetrol - DROVELIS (CAP); LYDISILKA (CAP) - PSUSA/00010938/202305**

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Applicant: Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.) (Drovelis), Estetra SRL (Lydisilka)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**16.1.16. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/202304**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.17. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/202304**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.18. Erenumab - AIMOVIG (CAP) - PSUSA/00010699/202305**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

**16.1.19. Febuxostat - ADENURIC (CAP) - PSUSA/00001353/202304**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

**16.1.20. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202304**

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Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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**16.1.21. Fulvestrant - FASLODEX (CAP) - PSUSA/00001489/202304**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

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**16.1.22. Glycopyrronium bromide, formoterol - BEVESPI AEROSPHERE (CAP) - PSUSA/00010739/202304**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

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**16.1.23. Golimumab - SIMPONI (CAP) - PSUSA/00001560/202304**

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

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**16.1.24. Hepatitis B surface antigen, CpG 1018 adjuvant - HEPLISAV B (CAP) - PSUSA/00010919/202305**

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Applicant: Dynavax GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

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**16.1.25. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/202304**

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Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

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**16.1.26. Linzagolix choline - YSELTLY (CAP) - PSUSA/00010998/202305**

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Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

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**16.1.27. Loncastuximab tesirine - ZYNLONTA (CAP) - PSUSA/00011027/202304**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Jirsová



Scope: Evaluation of a PSUSA procedure

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**16.1.28. Mitotane - LYSODREN (CAP) - PSUSA/00002075/202304**

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Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

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**16.1.29. Nintedanib<sup>52</sup> - OFEV (CAP) - PSUSA/00010319/202304**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

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**16.1.30. Nirsevimab - BEYFORTUS (CAP) - PSUSA/00011026/202304**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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**16.1.31. Parathyroid hormone - NATPAR (CAP) - PSUSA/00010591/202304**

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Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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**16.1.32. Pegcetacoplan - ASPAVELI (CAP) - PSUSA/00010974/202305**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

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**16.1.33. Pemigatinib - PEMAZYRE (CAP) - PSUSA/00010923/202304**

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Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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**16.1.34. Potassium citrate, potassium hydrogen carbonate - SIBNAYAL (CAP) - PSUSA/00010932/202304**

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Applicant: Advicenne

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<sup>52</sup> Respiratory indication only

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.35. Recombinant vesicular stomatitis virus - Zaire ebolavirus vaccine (live) - ERVEBO (CAP) - PSUSA/00010834/202305**

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Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.36. Remdesivir (Veklury) - VEKLURY (CAP) - PSUSA/00010840/202305**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

**16.1.37. Ripretinib - QINLOCK (CAP) - PSUSA/00010962/202305**

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Applicant: Deciphera Pharmaceuticals (Netherlands) B.V.

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

**16.1.38. Sacituzumab govitecan - TRODELVY (CAP) - PSUSA/00010959/202304**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.39. Selpercatinib - RETSEVMO (CAP) - PSUSA/00010917/202305**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.1.40. Somatrogon - NGENLA (CAP) - PSUSA/00010982/202304**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

**16.1.41. Tafamidis - VYNDAQEL (CAP) - PSUSA/00002842/202305**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

#### 16.1.42. Tirzepatide - MOUNJARO (CAP) - PSUSA/00011019/202305

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.43. Tixagevimab, cilgavimab - EVUSHELD (CAP) - PSUSA/00010992/202305

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

#### 16.1.44. Tucatinib - TUKYSA (CAP) - PSUSA/00010918/202304

Applicant: Seagen B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 16.1.45. Volanesorsen - WAYLIVRA (CAP) - PSUSA/00010762/202305

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.1.46. Zanubrutinib - BRUKINSA (CAP) - PSUSA/00010960/202305

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)**

#### 16.2.1. Bortezomib - BORTEZOMIB ACCORD (CAP); BORTEZOMIB FRESENIUS KABI (CAP); BORTEZOMIB HOSPIRA (CAP); BORTEZOMIB SUN (CAP); VELCADE (CAP); NAP - PSUSA/00000424/202304

Applicant: Accord Healthcare S.L.U. (Bortezomib Accord), Fresenius Kabi Deutschland GmbH (Bortezomib Fresenius Kabi), Pfizer Europe MA EEIG (Bortezomib Hospira), Sun Pharmaceutical Industries Europe B.V. (Bortezomib SUN), Janssen-Cilag International N.V. (VELCADE), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**16.2.2. Ivabradine - CORLENTOR (CAP); IVABRADINE ANPHARM (CAP); PROCORALAN (CAP); NAP - PSUSA/00001799/202304**

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Applicant: ANPHARM Przedsiębiorstwo Farmaceutyczne S.A. (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procoralan), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**16.2.3. Somatropin - NUTROPINAQ (CAP); OMNITROPE (CAP); NAP - PSUSA/00002772/202303**

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Applicant: Ipsen Pharma (NutropinAq), Sandoz GmbH (Omnitrope), various

PRAC Rapporteur: Karin Ernehlm

Scope: Evaluation of a PSUSA procedure

**16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only**

**16.3.1. Acarbose (NAP) - PSUSA/00000017/202303**

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Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

**16.3.2. Benzyl nicotinate, camphor, dimethyl sulfoxide, nonivamide, turpentine oil; nicoboxil, nonivamide (NAP) - PSUSA/00010584/202303**

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Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

**16.3.3. Deproteinised hemoderivative of calf blood; deproteinised hemoderivative of calf blood, macrogol 400 (NAP) - PSUSA/00010600/202303**

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Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

**16.3.4. Doxylamine (NAP) - PSUSA/00001174/202304**

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Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.3.5. Dronabinol, cannabidiol (NAP) - PSUSA/00010844/202304

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Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### 16.3.6. Enalapril (NAP) - PSUSA/00001211/202303

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Applicant(s): various

PRAC Lead: Mari Thörn

Scope: Evaluation of a PSUSA procedure

#### 16.3.7. Epinephrine, mepivacaine hydrochloride; mepivacaine, norepinephrine; mepivacaine (NAP) - PSUSA/00001979/202303

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Applicant(s): various

PRAC Lead: Karin Erneholm

Scope: Evaluation of a PSUSA procedure

#### 16.3.8. Estradiol; estradiol, prednisolone<sup>53</sup> (NAP) - PSUSA/00010441/202304

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Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

#### 16.3.9. Foscarnet (NAP) - PSUSA/00001472/202303

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Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### 16.3.10. Ivabradine, metoprolol (NAP) - PSUSA/00010381/202304

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Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.3.11. Lavender oil (NAP) - PSUSA/00010810/202304

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Applicant(s): various

PRAC Lead: Gudrun Thengilsdottir

Scope: Evaluation of a PSUSA procedure

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<sup>53</sup> Only cream/balm/emulsion for application in the female genital area

#### 16.3.12. Methylphenobarbital (NAP) - PSUSA/00002025/202303

Applicant(s): various

PRAC Lead: Benjamin Micallef

Scope: Evaluation of a PSUSA procedure

#### 16.3.13. Mometasone furoate, olopatadine (NAP) - PSUSA/00010957/202304

Applicant(s): various

PRAC Lead: Mari Thörn

Scope: Evaluation of a PSUSA procedure

#### 16.3.14. Ofloxacin<sup>54</sup> (NAP) - PSUSA/00002203/202304

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

#### 16.3.15. Pimecrolimus (NAP) - PSUSA/00002411/202303

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

#### 16.3.16. Piribedil (NAP) - PSUSA/00002436/202303

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### 16.3.17. Porfimer (NAP) - PSUSA/00010332/202304

Applicant(s): various

PRAC Lead: Petar Mas

Scope: Evaluation of a PSUSA procedure

#### 16.3.18. Rifamycin (NAP) - PSUSA/00002641/202304

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

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<sup>54</sup> Systemic use only

#### 16.3.19. Sodium tetradecyl sulphate (NAP) - PSUSA/00002767/202304

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Applicant(s): various

PRAC Lead: Jana Lukačičinová

Scope: Evaluation of a PSUSA procedure

#### 16.3.20. Triamcinolone<sup>55</sup> (NAP) - PSUSA/00010292/202303

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Applicant(s): various

PRAC Lead: Carla Torre

Scope: Evaluation of a PSUSA procedure

### 16.4. Follow-up to PSUR/PSUSA procedures

#### 16.4.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/LEG 057

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of a cumulative review of cases of hepatotoxicity and drug-induced liver injury (DILI) associated with ustekinumab use following the assessment of the PSUSA procedure PSUSA/00003085/202212 concluded in September 2023<sup>56</sup>

### 16.5. Variation procedure(s) resulting from PSUSA evaluation

None

### 16.6. Expedited summary safety reviews<sup>57</sup>

None

## 17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

### 17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>58</sup>

#### 17.1.1. Ketoconazole - Ketoconazole HRA (CAP) - EMEA/H/C/PSA/S/0109

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Applicant: HRA Pharma Rare Diseases

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<sup>55</sup> Intraocular formulations only

<sup>56</sup> Meeting held on 28-31 August 2023

<sup>57</sup> Submission of expedited summary safety reports for review in addition to the requirements for submission of PSUR(s) falling within the pandemic period and requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

<sup>58</sup> In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Petar Mas

Scope: Substantial amendment to a protocol for a prospective, multi-country, observational registry to collect clinical information on patients with endogenous Cushing's syndrome exposed to Ketoconazole (using the existing European Registry on Cushing's Syndrome (ERCUSYN)), to assess drug utilization pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of Ketoconazole

### **17.1.2. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/PSA/S/0108**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Substantial amendment to a PASS of paediatric patients initiating selumetinib in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with NF1 aged 3 years and above

### **17.1.3. Valproate<sup>59</sup> (NAP) - EMEA/H/N/PSP/J/0074.8**

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Applicant: Sanofi-Aventis Recherche & Développement (on behalf of a consortium)

PRAC Rapporteur: Jean-Michel Dogné

Scope: Responses to the 2nd RSI of the 2nd Interim report: Observational study to evaluate and identify the best practices for switching of valproate in clinical practice [MAH's response to PSP/J/0074.7]

## **17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>60</sup>**

### **17.2.1. Anifrolumab - SAPHNELO (CAP) - EMEA/H/C/004975/MEA 001.2**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Revised protocol for a non-imposed PASS Study D3461R00028: A multiple database study of the use (and safety) of anifrolumab in women with SLE during pregnancy.

### **17.2.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.10**

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Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.9 [post-approval registry Protocol PTC124-GD-0250-DMD: Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care] as per request for supplementary information (RSI) adopted in July 2023

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<sup>59</sup> Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium

<sup>60</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004



### [17.2.3. Baricitinib - OLUMIANT \(CAP\) - EMEA/H/C/004085/MEA 015.1](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 015 [submission of a protocol for study I4V-MC-B025: Rheumatologist and Dermatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant (baricitinib), a JAK1/2 Inhibitor] as per request for supplementary information (RSI) adopted in July 2023

### [17.2.4. Baricitinib - OLUMIANT \(CAP\) - EMEA/H/C/004085/MEA 016.1](#)

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 016 [Submission of a protocol for study I4V-MC-B038: Baricitinib Drug Utilisation Study: Assessment of Effectiveness of New Recommendations for Use Based on Secondary Data Sources in France, Germany, The Netherlands, and Sweden. This study aims to assess the utilisation of baricitinib in patients with RA, AA, or AD with respect to the new recommendations further to the completion of the Pharmacovigilance article 20 in the aRMMs (DHPC, Healthcare Professional educational materials, and Patient Alert Card)] as per request for supplementary information (RSI) adopted in July 2023

### [17.2.5. Bimekizumab - BIMZELX \(CAP\) - EMEA/H/C/005316/MEA 002.3](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: From Initial MAA: Bimekizumab real-world outcomes study: The goal of this study is to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO patients compared to PSO patients exposed to other biologics (e.g., anti TNF, anti-IL-23, but not anti IL 17)

### [17.2.6. Bimekizumab - BIMZELX \(CAP\) - EMEA/H/C/005316/MEA 004.2](#)

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Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: From Initial MAA: An observational cohort study to evaluate bimekizumab exposure during pregnancy. To monitor the safety of bimekizumab use in pregnancy

### [17.2.7. Coronavirus \(COVID-19\) vaccine \(ChAdOx1-S \[recombinant\]\) - VAXZEVRIA \(CAP\) - EMEA/H/C/005675/MEA 006.10](#)

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Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: From Initial MAA: COVID-19 Vaccines International Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy

**17.2.8. Coronavirus (COVID-19) vaccine (Ad26.COVID-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 007.1**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: From Initial MAA: COVID-19 Vaccines International Pregnancy Exposure Registry (C VIPER) (VAC31518COV4005), to assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COVID.S during pregnancy. (Cat.3 )

**17.2.9. Coronavirus (COVID-19) vaccine (Ad26.COVID-S, recombinant) - JCOVDEN (CAP) - EMEA/H/C/005737/MEA 077**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Results of the test made on samples from suspected TTS cases from study COV3001 in a platelet activation assay, namely PF4-induced platelet activation assay (PIPAA); the assay also tests in heparin independent conditions.

Platelet Factor 4-Induced Platelet Activation Assessment of Selected Samples from the VAC31518COV3001 Study. Title: A Randomised, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COVID.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

**17.2.10. Daridorexant - QUVIVIQ (CAP) - EMEA/H/C/005634/MEA 003.1**

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Applicant: Idorsia Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: To compare the maternal, foetal, and infant outcomes of women exposed to daridorexant during pregnancy to an unexposed control population

**17.2.11. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/MEA 011**

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Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: From II/0060: Title: Registry-based study to evaluate the long-term safety of dupilumab in children aged  $\geq 6$  months to  $<6$  years with moderate-to-severe Atopic Dermatitis using the PEDISTAD registry

**17.2.12. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 002.2**

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Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: From Initial MAA: PASS to characterize the risks and missing information outlined in this risk management plan and evaluate whether there are specific and/or unexpected patterns of adverse events

#### 17.2.13. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/MEA 004.2

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 004.1 [Submission of a protocol for a PASS to characterise the missing information use in pregnant woman outlined in the risk management plan] as per request for supplementary information (RSI) adopted in July 2023

#### 17.2.14. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 005.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 005.1 [protocol for study IM0471037: a PASS titled 'Long-term real-world safety of ozanimod – A PASS in patients diagnosed with ulcerative colitis'. This study is a category 3 study (required additional pharmacovigilance activity - UC indication) listed in the RMP version 3.0] as per the request for supplementary information (RSI) adopted in June 2023

#### 17.2.15. Respiratory syncytial virus vaccine (bivalent, recombinant) - ABRYSV0 (CAP) - EMEA/H/C/006027/MEA 002

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Title: A PASS of Guillain-Barré Syndrome (GBS) Following ABRYSVOTM Among Older Adults in the United States

#### 17.2.16. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 009.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 009 [Protocol for study P23-653 (non-imposed/non-interventional): Pregnancy Exposure and Outcomes for Women with Crohn's Disease Treated with Risankizumab. A comparative cohort study to describe risankizumab exposure in pregnant patients with Crohn's disease, and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with Crohn's disease without exposure to any treatments under investigation will also be conducted] as per request for supplementary information (RSI) adopted in June 2023.

#### 17.2.17. Somapacitan - SOGROYA (CAP) - EMEA/H/C/005030/MEA 005

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Martin Huber

Scope: From X/0006/G: Paediatric GHD register-based study: A non-interventional, observational, register-based study to investigate long-term safety and clinical parameters

of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice

#### 17.2.18. Tezepelumab - TEZSPIRE (CAP) - EMEA/H/C/005588/MEA 005

Applicant: AstraZeneca AB

PRAC Rapporteur: Eva Jirsová

Scope: From initial MAA An observational multi-country PASS to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking Tezepelumab

#### 17.2.19. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 004.5

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 004.4 [amendment to a previously agreed protocol for study P19-141: a long-term PASS of upadacitinib use in rheumatoid arthritis (RA) patients in the US in order to: 1) compare the incidence of malignancy, non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA; 2) describe the incidence rates of herpes zoster, opportunistic infections and evidence of drug-induced liver injury (DILI); 3) describe the incidence of the above outcomes in very elderly patients (aged  $\geq 75$  years); 4) characterise VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies] as per request for supplementary information (RSI) adopted in June 2023

#### 17.2.20. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 005.3

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Upadacitinib Drug Utilisation Study (DUS) for aRMM Effectiveness Evaluation to describe the baseline characteristics of new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of a bDMARD for comparison

#### 17.2.21. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 012.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of the Effectiveness of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis

### 17.2.22. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 016.2

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Title: Drug Utilization Study for Evaluation of the Effectiveness of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Sweden and Denmark

### 17.2.23. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 030

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Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: A Survey among Patients, Caregivers and Home Infusion Nurses based in the European Union to Assess their Awareness and Understanding of Educational Materials (EM) Supporting VPRIV Infusion at Home. Objectives: To determine whether patients/caregivers and home infusion nurses appropriately understand and implement the EM associated with VPRIV home infusion. Specifically, to assess the proportion of patients/caregivers and home infusion nurses who are aware of the EM; who understand the EM; and who use the EM. Safety concerns addressed: Infusion-related reactions, including allergic-type hypersensitivity reactions

## 17.3. Results of PASS imposed in the marketing authorisation(s)<sup>61</sup>

### 17.3.1. Levofloxacin – QUINSAIR (CAP) - EMEA/H/C/PSR/S/0046

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Final study report for a post-marketing, observational safety study of Quinsair (levofloxacin hemihydrate) in patients with cystic fibrosis (CF) to evaluate the long-term safety compared to other inhaled approved antibiotic therapies in CF patients

## 17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>62</sup>

### 17.4.1. Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/II/0054

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Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from non-interventional PASS study COMBINE-2 listed as a category 3 study in the RMP. This is a real-world evidence study to evaluate effectiveness of two drug regimen, antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor. The RMP version 6.0 has also been submitted in order to remove the important identified risk of "drug resistance"

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<sup>61</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>62</sup> In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

17.4.2. [Empagliflozin, linagliptin - GLYXAMBI \(CAP\) - EMEA/H/C/003833/WS2571/0055;](#)  
[Empagliflozin - JARDIANCE \(CAP\) - EMEA/H/C/002677/WS2571/0082;](#)  
[Empagliflozin, metformin - SYNJARDY \(CAP\) - EMEA/H/C/003770/WS2571/0076](#)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study 1245-0201. This is an observational PASS to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2i)-containing glucose lowering drugs. The RMP versions 22.0, 15.0 and 10.0 have also been submitted for Jardiance, Synjardy and Glyxambi, respectively

17.4.3. [Filgrastim - NIVESTIM \(CAP\) - EMEA/H/C/001142/II/0074/G](#)

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped application consisting of:

C.I.13: Submission of the final report from non-interventional PASS study ZOB-NIV-1513/C1121008, listed as a category 3 study in the RMP. This is a multinational, multi-centre, prospective, non-interventional, PASS in Healthy Donors (HDs) exposed to Nivestim (biosimilar filgrastim) for Haematopoietic Stem Cell (HSC) Mobilisation (NEST). The RMP version 12 has also been submitted.

C.I.11 for RMP: Submission of an updated RMP version 12.0 in order to align it with the reference product, Neupogen, RMP v. 6.3 dated June 2022

17.4.4. [Golimumab - SIMPONI \(CAP\) - EMEA/H/C/000992/II/0117/G](#)

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Grouped application consisting of:

C.I.13: Submission of the final report from study UC Nordic (MK-8259-013) listed as a category 3 study in the RMP. This is a Non-interventional Observational Longitudinal Post Authorisation Safety Study (PASS) of SIMPONI in Treatment of Ulcerative Colitis using Nordic National Health Registries.

C.I.13: Submission of the final report from study ENEIDA (MK-8259-042) listed as a category 3 study in the RMP. This is a PASS of Golimumab in ulcerative colitis (UC) Using the Spanish ENEIDA Registry. The RMP version 27.1 has also been submitted

17.4.5. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0241](#)

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Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report for the PSOLAR (C0168Z03) registry "A Multicenter, Open Registry of Patients with Psoriasis Who Are Candidates for Systemic Therapy Including Biologics: PSOLAR", listed as a category 3 study in the RMP (MEA114). This is an

international, multicenter, prospective observational registry for monitoring the long-term safety experience and clinical status of patients  $\geq 18$  years of age who are eligible to receive or are actively receiving any systemic therapies for psoriasis, including those currently receiving or planning to receive infliximab. The RMP version 21.1 has also been submitted

#### **17.4.6. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0053**

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Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC in order to update safety and efficacy information for the hepatocellular carcinoma (HCC) indication, based on interim results from study E7080-M000-508 (STELLAR), listed as a category 3 PASS in the RMP. This is a non-interventional multicentre, observational, phase 4 study to evaluate the safety and tolerability of lenvatinib in patients with advanced or unresectable HCC. RMP version 15.2 has also been submitted

#### **17.4.7. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0199**

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Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: Submission of the final report for study BE29950 (RIVAS), listed as a category 3 study in the RMP. This is a prospective, single center, secondary data use, long-term surveillance, non-interventional PASS with the objective to better characterise the risk profile of MabThera by collecting long term safety data in patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have been treated with rituximab (MabThera) or other available non-rituximab therapies. The RMP version 24.0 has also been submitted

### **17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation**

#### **17.5.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 080.9**

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Mari Thorn

Scope: Seventh annual interim report for P11-292 registry: a long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in paediatric patients with moderately to severely active Crohn's disease (CD) – CAPE

#### **17.5.2. Elasmomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 118**

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Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Interim report for PASS mRNA-1273-P920 (non-imposed/RMP); Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA 1273 booster vaccines in the United States

### 17.5.3. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.4

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Interim report for study EUPAS 29407 (category 3 study listed in the RMP): PASS to evaluate the risks of MDS/AML and SPM in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (Niraparib)

### 17.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.11

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Seventh annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice

### 17.5.5. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 001.8

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fifth interim report for PASS Study No. OP0005 (NINI); European non-interventional PASS related to the adherence to the cardiovascular risk minimization measures for romosozumab, by the EU-ADR Alliance

### 17.5.6. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 002.8

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Fifth interim report for PASS Study No. OP0004 (NINI); European non-interventional PASS related to serious cardiovascular adverse events of myocardial infarction and stroke for romosozumab by the EU-ADR Alliance to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions

### 17.5.7. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA 003.6

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: From Initial MAA: PASS Study No. OP0006 (NINI); European non-interventional PASS related to serious infections risk for romosozumab by the EU-ADR Alliance to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions



#### 17.5.8. Selumetinib - KOSELUGO (CAP) - EMEA/H/C/005244/SOB 004

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Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: First annual progress report for a non-interventional PASS in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above listed as specific obligation in Annex II-D: 'The applicant will conduct and submit the results of a non-interventional PASS in patients with NF1 who have been prescribed at least one dose of selumetinib and who are aged 3 to ≤18 years at the start of selumetinib treatment. A nested cohort of patients aged ≥8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively'

#### 17.5.9. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 013.4

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Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: First annual progress report for non-imposed non-interventional category 3 PASS study P20-390-825: Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

#### 17.6. Others

None

#### 17.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

#### 17.8. Ongoing Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

#### 17.9. Final Scientific Advice (Reports and Scientific Advice letters)

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

### 18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicine(s) listed below and the CHMP Rapporteur's assessment report, PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional

circumstances for the medicines listed below were recommended. As per the agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

## **18.1. Annual reassessments of the marketing authorisation**

### **18.1.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/003794/S/0066 (without RMP)**

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Applicant: Alexion Europe SAS

PRAC Rapporteur: Eamon O'Murchu

Scope: Annual reassessment of the marketing authorisation

### **18.1.2. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0042 (without RMP)**

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Applicant: BioMarin International Limited

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

### **18.1.3. Eladocagene exuparvovec - UPSTAZA (CAP) - EMEA/H/C/005352/S/0017 (without RMP)**

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Applicant: PTC Therapeutics International Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

### **18.1.4. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0057 (without RMP)**

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Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

### **18.1.5. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0081 (without RMP)**

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Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

### **18.1.6. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0095 (without RMP)**

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Annual reassessment of the marketing authorisation

#### **18.1.7. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0090 (without RMP)**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

### **18.2. Conditional renewals of the marketing authorisation**

#### **18.2.1. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/R/0070 (with RMP)**

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Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Jo Robays

Scope: Conditional renewal of the marketing authorisation

#### **18.2.2. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0058 (with RMP)**

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Applicant: Holostem, ATMP

PRAC Rapporteur: Eamon O'Murchu

Scope: Conditional renewal of the marketing authorisation

#### **18.2.3. Parathyroid hormone - NATPAR (CAP) - EMEA/H/C/003861/R/0054 (without RMP)**

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Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Rhea Fitzgerald

Scope: Conditional renewal of the marketing authorisation

#### **18.2.4. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/R/0013 (without RMP)**

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Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

#### **18.2.5. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/R/0026 (without RMP)**

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Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

### **18.3. Renewals of the marketing authorisation**

#### **18.3.1. Ambrisentan - AMBRISENTAN MYLAN (CAP) - EMEA/H/C/004985/R/0009 (without RMP)**

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Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

### 18.3.2. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/R/0018 (without RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: 5-year renewal of the marketing authorisation

### 18.3.3. Pegfilgrastim - GRASUSTEK (CAP) - EMEA/H/C/004556/R/0014 (with RMP)

Applicant: Juta Pharma GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

### 18.3.4. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/R/0022 (without RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: 5-year renewal of the marketing authorisation

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 27-30 November 2023 PRAC meeting, which was held in-person.

An asterisk (\*) after the role, in the second column, signals that the member/alternate attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus <sup>a,b</sup>	Chair	The Netherlands	No interests declared	
Jan Neuhauser <sup>a</sup>	Member	Austria	No interests declared	
Sonja Hrabcik <sup>a,b</sup>	Alternate*	Austria	No interests declared	
Jean-Michel Dogné <sup>a,b</sup>	Member	Belgium	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jo Robays <sup>a</sup>	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva <sup>a,b</sup>	Member	Bulgaria	No interests declared	
Nikica Mirošević Skvrce <sup>a,b</sup>	Member	Croatia	No interests declared	
Petar Mas <sup>a,b</sup>	Alternate	Croatia	No interests declared	
Elena Kaisis <sup>b</sup>	Member*	Cyprus	No interests declared	
Panagiotis Psaras <sup>a,b</sup>	Alternate	Cyprus	No interests declared	
Eva Jirsová <sup>a,b</sup>	Member	Czechia	No interests declared	
Jana Lukacisinova <sup>a,b</sup>	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen <sup>a,b</sup>	Member	Denmark	No interests declared	
Karin Erneholm	Alternate	Denmark	No interests declared	
Maia Uusküla <sup>a</sup>	Member	Estonia	No interests declared	
Kirsti Villikka <sup>a,b</sup>	Member	Finland	No interests declared	
Kimmo Jaakkola <sup>a,b</sup>	Alternate	Finland	No interests declared	
Tiphaine Vaillant <sup>a</sup>	Member	France	No interests declared	
Nathalie Gault <sup>a,b</sup>	Alternate	France	No interests declared	
Martin Huber <sup>a,b</sup>	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer <sup>a,b</sup>	Alternate	Germany	No participation in final deliberations and voting on:	17.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.11
Sofia Trantza <sup>a,b</sup>	Member	Greece	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Georgia Gkegka <sup>a</sup>	Alternate*	Greece	No interests declared	
Julia Pallos <sup>a,b</sup>	Member	Hungary	No participation in final deliberations and voting on:	<p>5.3.6. Apixaban - ELIQUIS (CAP) - EMEA/H/C/00 2148/X/0089/G</p> <p>15.2.3. Dasatinib - SPRYCEL (CAP) - EMEA/H/C/00 0709/II/0090</p> <p>17.2.14. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/00 4835/MEA 005.2</p> <p>17.5.4. Nivolumab - OPDIVO (CAP) - EMEA/H/C/00 3985/MEA 008.11</p>
Melinda Palfi <sup>a</sup>	Alternate*	Hungary	No interests declared	
Guðrún Stefánsdóttir <sup>a</sup>	Member	Iceland	No participation in final deliberations and voting on:	15.3.26. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/00 5522/II/0010/G
Gudrun Þengilsdóttir <sup>a</sup>	Alternate *	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald <sup>a,b</sup>	Member	Ireland	No interests declared	
Eamon O Murchu <sup>a</sup>	Alternate	Ireland	No interests declared	
Amelia Cupelli <sup>a</sup>	Member	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Valentina Di Giovanni <sup>a,b</sup>	Alternate*	Italy	No interests declared	
Zane Neikena <sup>a,b</sup>	Member	Latvia	No interests declared	
Lina Seibokiene <sup>a</sup>	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain <sup>a,b</sup>	Member	Luxembourg	No participation in final deliberations and voting on:	3.3.1 EMA/H/A-31/1526
Anne-Cécile Vuillemin <sup>a</sup>	Alternate*	Luxembourg	No interests declared	
John Joseph Borg <sup>a</sup>	Member	Malta	No interests declared	
Benjamin Micallef <sup>a</sup>	Alternate*	Malta	No interests declared	
Menno van der Elst <sup>a</sup>	Member	Netherlands	No interests declared	
Liana Martirosyan <sup>a</sup>	Alternate	Netherlands	No interests declared	
Liana Martirosyan <sup>b</sup>	Member	Netherlands	No interests declared	
Bianca Mulder <sup>b</sup>	Alternate	Netherlands	No interests declared	
David Olsen <sup>a,b</sup>	Member	Norway	No participation in final deliberations and voting on:	3.3.1 EMA/H/A-31/1526  6.3.2. Ciprofloxacin (NAP) - PSUSA/00000 775/202304  16.3.1. Acarbose (NAP) - PSUSA/00000 017/202303
Pernille Harg <sup>a,b</sup>	Alternate	Norway	No interests declared	
Adam Przybylkowski <sup>a</sup>	Member	Poland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ana Sofia Diniz Martins <sup>a</sup>	Member	Portugal	No interests declared	
Carla Torre <sup>a</sup>	Alternate	Portugal	No interests declared	
Roxana Dondera <sup>a</sup>	Member	Romania	No interests declared	
Irina Sandu <sup>a,b</sup>	Alternate*	Romania	No interests declared	
Anna Mareková <sup>a,b</sup>	Member	Slovakia	No interests declared	
Miroslava Gocova <sup>a,b</sup>	Alternate*	Slovakia	No interests declared	
Polona Golmajer <sup>a,b</sup>	Member	Slovenia	No interests declared	
Maria del Pilar Rayon <sup>a,b</sup>	Member	Spain	No interests declared	
Monica Martinez Redondo <sup>a,b</sup>	Alternate	Spain	No interests declared	
Ulla Wändel Liminga <sup>a,b</sup>	Member	Sweden	No interests declared	
Mari Thorn <sup>a,b</sup>	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano <sup>a</sup>	Member*	Independent scientific expert	No interests declared	
Milou Daniel Drici <sup>a</sup>	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro <sup>a</sup>	Member	Independent scientific expert	No interests declared	
Patricia McGettigan <sup>a,b</sup>	Member*	Independent scientific expert	No interests declared	
Tania Schink <sup>a</sup>	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.3. Exenatide - BYDUREON (CAP) - EMEA/H/C/00 2020/SDA/03 0, BYETTA (CAP) - EMEA/H/C/00 0698/SDA/05 0; Dulaglutide - TRULICITY (CAP) - EMEA/H/C/00 2825/SDA/01



Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>0; Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/00 4243/SDA/00 9; Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/00 2445/SDA/01 7; liraglutide - SAXENDA (CAP) - EMEA/H/C/00 3780/SDA/02 0, VICTOZA (CAP) - EMEA/H/C/00 1026/SDA/04 0, XULTOPHY (CAP) - EMEA/H/C/00 2647/SDA/00 6; Semaglutide - OZEMPIC (CAP) - EMEA/H/C/00 4174/SDA/00 8, RYBELSUS (CAP) - EMEA/H/C/00 4953/SDA/01 3, WEGOVY (CAP) - EMEA/H/C/00 5422/SDA/00 7;</p> <p>17.5.5. Romosozumab - EVENITY (CAP) - EMEA/H/C/00 4465/MEA 001.8</p> <p>17.5.6. Romosozumab - EVENITY (CAP) - EMEA/H/C/00 4465/MEA 002.8</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				17.5.7. Romosozumab - EVENITY (CAP) - EMEA/H/C/004465/MEA003.6
Hedvig Nordeng <sup>a</sup>	Member	Independent scientific expert	No interests declared	
Roberto Frontini <sup>a,b</sup>	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messana <sup>a</sup>	Alternate*	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak <sup>a</sup>	Alternate	Patients' Organisation Representative	No interests declared	
Christian Gartner <sup>a</sup>	Expert	Austria	No interests declared	
Els Beghein <sup>a</sup>	Expert	Belgium	No interests declared	
Laurence de Fays <sup>a</sup>	Expert	Belgium	No interests declared	
Veronika Deščiková <sup>a</sup>	Expert	Czech Republic	No interests declared	
Michaela Dlouhá <sup>a</sup>	Expert	Czech Republic	No interests declared	
Petra Kaftanová <sup>a</sup>	Expert	Czech Republic	No interests declared	
Lucie Skálová <sup>a</sup>	Expert	Czech Republic	No interests declared	
Thalia Marie Blicher <sup>a</sup>	Expert	Denmark	No interests declared	
Alexander Braathen <sup>a</sup>	Expert	Denmark	No interests declared	
Nicklas Hasselblad Lundstrøm <sup>a</sup>	Expert	Denmark	No interests declared	
Mette Hjorslev Knudgaard <sup>a</sup>	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Per Sindahl <sup>b</sup>	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen <sup>a,b</sup>	Expert	Denmark	No restrictions applicable to this meeting	
Louise Wenzel-Petersen <sup>a</sup>	Expert	Denmark	No interests declared	
Katrin Kurvits <sup>a</sup>	Expert	Estonia	No interests declared	
Indrek Soosaar <sup>a</sup>	Expert	Estonia	No interests declared	
Helve Vestman <sup>a</sup>	Expert	Estonia	No interests declared	
Nicolas Camhaji <sup>a</sup>	Expert	France	No restrictions applicable to this meeting	
Vincent Gazin <sup>a</sup>	Expert	France	No interests declared	
Nathalie Morgensztejn <sup>a</sup>	Expert	France	No interests declared	
Stéphane Personne <sup>a</sup>	Expert	France	No interests declared	
Laure Tiquet <sup>a</sup>	Expert	France	No interests declared	
Aurélié Vitores <sup>a</sup>	Expert	France	No interests declared	
Dennis Lex <sup>a</sup>	Expert	Germany	No interests declared	
Karin Seifert <sup>a</sup>	Expert	Germany	No interests declared	
Bernadett Murárik <sup>a</sup>	Expert	Hungary	No restrictions applicable to this meeting	
Eleanor Carey <sup>a</sup>	Expert	Ireland	No interests declared	
Clare Foley <sup>a</sup>	Expert	Ireland	No interests declared	
Ronan Grimes <sup>a</sup>	Expert	Ireland	No interests declared	
Carlo Colosimo <sup>b</sup>	Expert	Italy	No restrictions against giving the SAG	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			report for Valproate (EMA/H/N/PS R/J/0043)	
Gunta Paušena <sup>a</sup>	Expert	Latvia	No interests declared	
Elita Poplavska <sup>a</sup>	Expert	Latvia	No interests declared	
Alexandra Branchu <sup>a</sup>	Expert	Luxembourg	No participation in final deliberations and voting on:	3.3.1 EMA/H/A-31/1526
Martine Trauffler <sup>a</sup>	Expert	Luxembourg	No interests declared	
Bianca Mulder <sup>a</sup>	Expert	Netherlands	No interests declared	
Evelyn Mulder-Olthof <sup>a</sup>	Expert	Netherlands	No interests declared	
Anne Slomp <sup>a</sup>	Expert	Netherlands	No restrictions applicable to this meeting	
Lars Peter Austdal <sup>a</sup>	Expert	Norway	No interests declared	
Susanne Dertz <sup>a</sup>	Expert	Norway	No interests declared	
Eva Cantarero <sup>a</sup>	Expert	Spain	No interests declared	
Natividad Galiana <sup>a</sup>	Expert	Spain	No restrictions applicable to this meeting	
Rebeca González <sup>a</sup>	Expert	Spain	No interests declared	
Charlotte Backman <sup>a,b</sup>	Expert	Sweden	No interests declared	
Anna Schölin <sup>a</sup>	Expert	Sweden	No interests declared	

A representative from the European Commission attended the meeting

Meeting run with support from relevant EMA staff

Experts were evaluated against the agenda topics or activities they participated in.

## 20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[List of abbreviations used in EMA human medicines scientific committees and CMDh documents, and in relation to EMA's regulatory activities](#)

## 21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

### **EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures**

(Items 2 and 3 of the PRAC minutes)

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, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

### **Risk Management Plans (RMPs)**

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

### **Assessment of Periodic Safety Update Reports (PSURs)**

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation. PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

### **Post-authorisation Safety Studies (PASS)**

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:

<https://www.ema.europa.eu/en>