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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of PRAC meeting on 04 – 07 March 2024

Chair: Sabine Straus – Vice-Chair: Martin Huber

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Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

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Table of contents

1.	Introduction	12
1.1.	Welcome and declarations of interest of members, alternates and experts	12
1.2.	Agenda of the meeting on 04-07 March 2024	12
1.3.	Minutes of the previous meeting on 05-08 February 2024.....	12
2.	EU referral procedures for safety reasons: urgent EU procedures	12
2.1.	Newly triggered procedures	12
2.2.	Ongoing procedures	12
2.3.	Procedures for finalisation.....	13
3.	EU referral procedures for safety reasons: other EU referral procedures	13
3.1.	Newly triggered procedures	13
3.2.	Ongoing procedures	13
3.3.	Procedures for finalisation.....	13
3.4.	Re-examination procedures.....	13
3.5.	Others	13
4.	Signals assessment and prioritisation	13
4.1.	New signals detected from EU spontaneous reporting systems	13
4.1.1.	Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP)	13
4.2.	New signals detected from other sources	14
4.3.	Signals follow-up and prioritisation	14
4.3.1.	Abemaciclib – VERZENIOS (CAP) - EMEA/H/C/004302/SDA/004; Palbociclib – IBRANCE (CAP) - EMEA/H/C/003853/SDA/005; Ribociclib – KISQALI (CAP) - EMEA/H/C/004213/SDA/006	14
4.3.2.	Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/131	15
4.3.3.	Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP) - EMEA/H/C/002825/SDA/015; exenatide – BYDUREON (CAP) - EMEA/H/C/002020/SDA/031, BYETTA (CAP) - EMEA/H/C/000698/SDA/051; insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/SDA/003; liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/SDA/021, VICTOZA (CAP) - EMEA/H/C/001026/SDA/041; insulin glargine, lixisenatide – SULIQUA (CAP) - EMEA/H/C/004243/SDA/010; lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/SDA/018; semaglutide – OZEMPIC (CAP) - EMEA/H/C/004174/SDA/009, RYBELSUS (CAP) - EMEA/H/C/004953/SDA/014, WEGOVY (CAP) - EMEA/H/C/005422/SDA/008; tirzepatide – MOUNJARO (CAP) - EMEA/H/C/005620/SDA/006	15
4.3.4.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/068.....	17
4.4.	Variation procedure(s) resulting from signal evaluation	17
5.	Risk management plans (RMPs)	18
5.1.	Medicines in the pre-authorisation phase	18

5.1.1.	Apadamtase alfa - (CAP MAA) - EMEA/H/C/006198, Orphan.....	18
5.1.2.	Beremagene geperpavec - (CAP MAA) - EMEA/H/C/006330, PRIME, Orphan	18
5.1.3.	Dasiglucagon - (CAP MAA) - EMEA/H/C/006214.....	18
5.1.4.	Fidanacogene elaparvovec - (CAP MAA) - EMEA/H/C/004774, PRIME.....	18
5.1.5.	RdESAT-6, rCFP-10 - (CAP MAA) - EMEA/H/C/006177	18
5.1.6.	Zolbetuximab - (CAP MAA) - EMEA/H/C/005868, Orphan.....	18
5.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	18
5.3.	Medicines in the post-authorisation phase – CHMP-led procedures	19
5.3.1.	Mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/II/0170/G.....	19
6.	Periodic safety update reports (PSURs)	19
6.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	19
6.1.1.	Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202307	20
6.1.2.	Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202308.....	20
6.1.3.	Dengue tetravalent vaccine (live, attenuated) - DENGUE TETRAVALENT VACCINE (Art 58) - EMEA/H/W/005362/PSUV/0011	21
6.1.4.	Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202307	21
6.1.5.	Dengue tetravalent vaccine (live, attenuated) - QDENG A (CAP) - PSUSA/00011034/202308	22
6.1.6.	Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202308.....	23
6.1.7.	Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202308.....	23
6.1.8.	Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202307	24
6.1.9.	Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202308	24
6.1.10.	Voxelotor - OXBRYTA (CAP) - PSUSA/00010983/202308	25
6.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	26
6.2.1.	Leuprorelin - CAMCEVI (CAP); NAP - PSUSA/00010877/202307	26
6.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	27
6.3.1.	Anastrozole (NAP) - PSUSA/00000210/202308.....	27
6.3.2.	Atorvastatin, ezetimibe (NAP) – PSUSA/00010385/202307	28
6.3.3.	Paracetamol, tramadol (NAP) - PSUSA/00002310/202308	28
6.3.4.	Quetiapine (NAP) - PSUSA/00002589/202307	29
6.4.	Follow-up to PSUR/PSUSA procedures	30
6.4.1.	Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/LEG 008	30
6.5.	Variation procedure(s) resulting from PSUSA evaluation	31
6.5.1.	Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0027.....	31
6.6.	Expedited summary safety reviews	31

7.	Post-authorisation safety studies (PASS)	31
7.1.	Protocols of PASS imposed in the marketing authorisation(s).....	31
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	32
7.3.	Results of PASS imposed in the marketing authorisation(s).....	32
7.4.	Results of PASS non-imposed in the marketing authorisation(s).....	32
7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	32
7.6.	Others	32
7.7.	New Scientific Advice	32
7.8.	Ongoing Scientific Advice	32
7.9.	Final Scientific Advice (Reports and Scientific Advice letters)	32
8.	Renewals of the marketing authorisation, conditional renewal and annual reassessments	32
8.1.	Annual reassessments of the marketing authorisation	32
8.2.	Conditional renewals of the marketing authorisation	32
8.3.	Renewals of the marketing authorisation	33
9.	Product related pharmacovigilance inspections	33
9.1.	List of planned pharmacovigilance inspections.....	33
9.2.	Ongoing or concluded pharmacovigilance inspections.....	33
9.3.	Others	33
10.	Other safety issues for discussion requested by CHMP or EMA	33
10.1.	Safety related variations of the marketing authorisation.....	33
10.2.	Timing and message content in relation to Member States' safety announcements	33
10.3.	Other requests.....	33
10.4.	Scientific Advice	33
11.	Other safety issues for discussion requested by the Member States	33
11.1.	Other requests.....	33
11.1.1.	Xylitol, magnesium sulfate heptahydrate, potassium chloride, procaine hydrochloride (NAP)	33
11.1.2.	Valproate (NAP) - NL/H/xxxx/WS/794	34
11.2.	Safety related variations of the marketing authorisation.....	35
12.	Organisational, regulatory and methodological matters	35
12.1.	Mandate and organisation of PRAC.....	35
12.1.1.	PRAC membership	35
12.1.2.	Vote by proxy	35
12.2.	Coordination with EMA Scientific Committees or CMDh-v	35

12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	35
12.4.	Cooperation within the EU regulatory network	36
12.4.1.	Health threats and EMA Emergency Task Force (ETF) activities - update.....	36
12.5.	Cooperation with International Regulators.....	36
12.6.	Contacts of PRAC with external parties and interaction with the Interested Parties to the Committee.....	36
12.7.	PRAC work plan	36
12.8.	Planning and reporting	36
12.9.	Pharmacovigilance audits and inspections	36
12.9.1.	Pharmacovigilance systems and their quality systems	36
12.9.2.	Pharmacovigilance inspections	36
12.9.3.	Pharmacovigilance audits.....	36
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list	36
12.10.1.	Periodic safety update reports	36
12.10.2.	Granularity and Periodicity Advisory Group (GPAG)	37
12.10.3.	PSURs repository	37
12.10.4.	Union reference date list – consultation on the draft list	37
12.11.	Signal management	37
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group	37
12.12.	Adverse drug reactions reporting and additional monitoring.....	37
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	37
12.12.2.	Additional monitoring	37
12.12.3.	List of products under additional monitoring – consultation on the draft list	37
12.13.	EudraVigilance database.....	38
12.13.1.	Activities related to the confirmation of full functionality	38
12.13.2.	EudraVigilance annual report 2023.....	38
12.14.	Risk management plans and effectiveness of risk minimisations.....	38
12.14.1.	Risk management systems	38
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations	38
12.15.	Post-authorisation safety studies (PASS)	38
12.15.1.	Post-authorisation Safety Studies – imposed PASS	38
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS	38
12.16.	Community procedures.....	38
12.16.1.	Referral procedures for safety reasons	38
12.17.	Renewals, conditional renewals, annual reassessments.....	38
12.18.	Risk communication and transparency	38
12.18.1.	Public participation in pharmacovigilance	38
12.18.2.	Safety communication	39

12.19.	Continuous pharmacovigilance	39
12.19.1.	Incident management	39
12.20.	Impact of pharmacovigilance activities	39
12.20.1.	GVP Module XVI (Rev.3) on Risk Minimisation Measures: post-public consultation draft Addendum II on Methods for Effectiveness Evaluation	39
12.20.2.	Joint Heads of Medicines Agencies (HMA)/European Medicines Agency (EMA) Multistakeholder workshop on Patient Registries.....	39
12.21.	Others	39
12.21.1.	Amendments to the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities - update.....	39
13.	Any other business	40
14.	Annex I – Signals assessment and prioritisation	40
14.1.	New signals detected from EU spontaneous reporting systems	40
14.1.1.	Acetazolamide (NAP).....	40
14.1.2.	Bumetanide (NAP)	40
14.1.3.	Dupilumab – DUPIXENT (CAP).....	40
14.1.4.	Entrectinib – ROZLYTREK (CAP).....	41
14.1.5.	Epcoritamab – TEPKINLY (CAP)	41
14.1.6.	Glofitamab – COLUMVI (CAP)	41
14.2.	New signals detected from other sources	41
15.	Annex I – Risk management plans	41
15.1.	Medicines in the pre-authorisation phase	41
15.1.1.	Dasatinib - (CAP MAA) - EMEA/H/C/006251	41
15.1.2.	Dimethyl fumarate - (CAP MAA) - EMEA/H/C/006471	42
15.1.3.	Dimethyl fumarate - (CAP MAA) - EMEA/H/C/006500	42
15.1.4.	Dimethyl fumarate - EMEA/H/C/006397	42
15.1.5.	Rituximab - (CAP MAA) - EMEA/H/C/006224	42
15.1.6.	Ustekinumab - (CAP MAA) - EMEA/H/C/005918.....	42
15.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	42
15.2.1.	Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0060	42
15.2.2.	Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0091	42
15.2.3.	Sacituzumab govitecan - TRODELVY (CAP) - EMEA/H/C/005182/II/0031	42
15.2.4.	Tocofersolan - VEDROP (CAP) - EMEA/H/C/000920/II/0047	43
15.3.	Medicines in the post-authorisation phase – CHMP-led procedures	43
15.3.1.	Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/X/0036/G	43
15.3.2.	Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0047.....	43
15.3.3.	Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/II/0011	44
15.3.4.	Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0044	44

15.3.5.	Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0044/G	44
15.3.6.	Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0052	45
15.3.7.	Budesonide, formoterol fumarate dihydrate - BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP) - EMEA/H/C/004882/II/0012/G	45
15.3.8.	Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/X/0033.....	45
15.3.9.	Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0015.....	46
15.3.10.	Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/X/0080/G.....	46
15.3.11.	Dengue tetravalent vaccine (live, attenuated) - DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED) TAKEDA (Art 58) - EMEA/H/W/005362/WS2593/0012; Dengue tetravalent vaccine (live, attenuated) - QDENGGA (CAP) - EMEA/H/C/005155/WS2593/0013	46
15.3.12.	Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0116	47
15.3.13.	Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/II/0057/G	47
15.3.14.	Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0064	47
15.3.15.	Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0014, Orphan	48
15.3.16.	Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0063.....	48
15.3.17.	Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0005	48
15.3.18.	Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0022/G, Orphan	48
15.3.19.	Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0037	49
15.3.20.	Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0031/G.....	49
15.3.21.	Ganaxolone - ZTALMY (CAP) - EMEA/H/C/005825/II/0005, Orphan.....	50
15.3.22.	Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/II/0019, Orphan.....	50
15.3.23.	Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0133/G.....	50
15.3.24.	Irinotecan hydrochloride trihydrate - ONIVYDE PEGYLATED LIPOSOMAL (CAP) - EMEA/H/C/004125/II/0034, Orphan.....	51
15.3.25.	Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/II/0025	51
15.3.26.	Osilodrostat - ISTURISA (CAP) - EMEA/H/C/004821/II/0017/G, Orphan	51
15.3.27.	Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/II/0019/G, Orphan.....	52
15.3.28.	Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0053/G.....	52
15.3.29.	Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0045.....	52
15.3.30.	Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0078	52
15.3.31.	Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/II/0044	53
15.3.32.	Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0028.....	53
15.3.33.	Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0018, Orphan	53
15.3.34.	Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0100.....	54
15.3.35.	Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/X/0006/G.....	54
15.3.36.	Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/II/0054	54
15.3.37.	Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0121	55
15.3.38.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0201	55

16. Annex I - Periodic safety update reports (PSURs) 55

16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	55
16.1.1. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202307	55
16.1.2. Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202308	56
16.1.3. Bimekizumab - BIMZELX (CAP) - PSUSA/00010953/202308.....	56
16.1.4. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202307	56
16.1.5. Catridecacog - NOVOTHIRTEEN (CAP) - PSUSA/00010034/202307	56
16.1.6. Corifollitropin alfa - ELONVA (CAP) - PSUSA/00000875/202307.....	56
16.1.7. Difelikefalin - KAPRUVIA (CAP) - PSUSA/00010995/202308	56
16.1.8. Eptinezumab - VYEPTI (CAP) - PSUSA/00010966/202308.....	56
16.1.9. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202308	57
16.1.10. Evolocumab - REPATHA (CAP) - PSUSA/00010405/202307	57
16.1.11. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202308.....	57
16.1.12. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202308	57
16.1.13. Hydrocortisone - ALKINDI (CAP) - PSUSA/00010674/202308	57
16.1.14. Ibuprofen - PEDEA (CAP) - PSUSA/00001712/202307	57
16.1.15. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202308.....	57
16.1.16. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202308.....	58
16.1.17. Lenacapavir - SUNLENCA (CAP) - PSUSA/00011012/202308	58
16.1.18. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202308	58
16.1.19. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202307	58
16.1.20. Melphalan flufenamide - PEPAXTI (CAP) - PSUSA/00011013/202308.....	58
16.1.21. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - PSUSA/00002017/202307..	58
16.1.22. Mitapivat - PYRUKYND (CAP) - PSUSA/00011025/202308.....	58
16.1.23. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202308.....	59
16.1.24. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202308	59
16.1.25. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202308.....	59
16.1.26. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202308.....	59
16.1.27. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/202307	59
16.1.28. Saxagliptin – ONGLYZA (CAP); saxagliptin, metformin - KOMBOGLYZE (CAP) - PSUSA/00002685/202307	59
16.1.29. Sotrovimab - XEVUDY (CAP) - PSUSA/00010973/202308	59
16.1.30. Sutimlimab - ENJAYMO (CAP) - PSUSA/00011023/202308.....	60
16.1.31. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202307.....	60
16.1.32. Teclistamab - TECVAYLI (CAP) - PSUSA/00011010/202308.....	60
16.1.33. Temozolomide - TEMODAL (CAP) - PSUSA/00002886/202307	60

16.1.34.	Tisagenlecleucel - KYMRIAHA (CAP) - PSUSA/00010702/202308	60
16.1.35.	Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202307.....	60
16.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	61
16.2.1.	Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/202307	61
16.2.2.	Eflornithine - VANIQA (CAP); NAP - PSUSA/00001202/202307	61
16.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	61
16.3.1.	Aciclovir, hydrocortisone (NAP) - PSUSA/00009004/202307.....	61
16.3.2.	Colchicine (NAP) - PSUSA/00000858/202307	61
16.3.3.	Donepezil, memantine (NAP) - PSUSA/00011039/202307.....	61
16.3.4.	Ezetimibe, rosuvastatin (NAP) - PSUSA/00010271/202307	61
16.3.5.	Fenofibrate (NAP) - PSUSA/00001362/202307	62
16.3.6.	Indometacin (NAP) - PSUSA/00001738/202307.....	62
16.3.7.	Inosine pranobex (NAP) - PSUSA/00010425/202308.....	62
16.3.8.	Niclosamide (NAP) - PSUSA/00002151/202308	62
16.3.9.	Ribavirin (NAP) - PSUSA/00010007/202307.....	62
16.4.	Follow-up to PSUR/PSUSA procedures	62
16.5.	Variation procedure(s) resulting from PSUSA evaluation	62
16.5.1.	Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0254	62
16.6.	Expedited summary safety reviews	63
17.	Annex I – Post-authorisation safety studies (PASS)	63
17.1.	Protocols of PASS imposed in the marketing authorisation(s).....	63
17.1.1.	Blinatumomab - Blincyto (CAP) - EMEA/H/C/PSA/S/0111.....	63
17.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	63
17.2.1.	Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/MEA 002.7	63
17.2.2.	Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/MEA 003	63
17.2.3.	Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/MEA 007.4	64
17.2.4.	Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.5.....	64
17.2.5.	Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.4	64
17.2.6.	Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.9	64
17.2.7.	Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.4	64
17.2.8.	Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.5.....	64
17.2.9.	Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 001.3.....	65
17.2.10.	Voclosporin - LUPKYNIS (CAP) - EMEA/H/C/005256/MEA 002.2	65
17.3.	Results of PASS imposed in the marketing authorisation(s).....	65
17.3.1.	Acridinium - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP); acridinium, formoterol fumarate dihydrate – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - EMEA/H/C/PSR/S/0047	65

17.4.	Results of PASS non-imposed in the marketing authorisation(s).....	66
17.4.1.	Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0033/G	66
17.4.2.	Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0096	66
17.4.3.	Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0081	66
17.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	66
17.5.1.	Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 021.1	66
17.5.2.	Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.16.....	67
17.5.3.	Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.5.....	67
17.5.4.	Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009.2	67
17.5.5.	Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.7	67
17.5.6.	Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 005.1.....	67
17.5.7.	Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.5.....	68
17.5.8.	Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009.4.....	68
17.5.9.	Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.9	68
17.5.10.	Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.15.....	68
17.5.11.	Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.2	68
17.5.12.	Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 003.1.....	68
17.5.13.	Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.7.....	69
17.5.14.	Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 003.2	69
17.5.15.	Human C1-esterase inhibitor - CINRYZE (CAP) - EMEA/H/C/001207/MEA 021.1	69
17.5.16.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.6.....	69
17.5.17.	Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.7	70
17.5.18.	Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/ANX 001.....	70
17.5.19.	Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.4	70
17.5.20.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.6	70
17.5.21.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.8	70
17.5.22.	Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/MEA 003.9	71
17.5.23.	Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.6	71
17.5.24.	Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.8.....	71
17.5.25.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.5	71
17.5.26.	Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 029.....	71
17.5.27.	Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005.4.....	72
17.6.	Others	72
17.7.	New Scientific Advice	72
17.8.	Ongoing Scientific Advice	72
17.9.	Final Scientific Advice (Reports and Scientific Advice letters)	72

18.	Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments	72
18.1.	Annual reassessments of the marketing authorisation	72
18.1.1.	Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0064 (without RMP).....	72
18.2.	Conditional renewals of the marketing authorisation	73
18.2.1.	Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0020 (without RMP)	73
18.2.2.	Futibatinib - LYTGObI (CAP) - EMEA/H/C/005627/R/0003 (without RMP).....	73
18.2.3.	Glofitamab - COLUMVI (CAP) - EMEA/H/C/005751/R/0003 (with RMP)	73
18.3.	Renewals of the marketing authorisation	73
18.3.1.	Angiotensin II - GIAPREZA (CAP) - EMEA/H/C/004930/R/0027 (without RMP)	73
18.3.2.	Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/R/0037 (without RMP)	73
18.3.3.	Deferasirox - DEFERASIROX MYLAN (CAP) - EMEA/H/C/005014/R/0013 (without RMP)	73
18.3.4.	Trientine - CUFENCE (CAP) - EMEA/H/C/004111/R/0016 (without RMP).....	73
19.	Annex II – List of participants	74
20.	Annex III - List of acronyms and abbreviations	81
21.	Explanatory notes	81

1. Introduction

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

The Chairperson opened the 04-07 March 2024 meeting by welcoming all participants. The meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and 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.

1.2. Agenda of the meeting on 04-07 March 2024

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 05-08 February 2024

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 05-08 February 2024 were published on the EMA website on 09 April 2024 ([EMA/PRAC/122241/2024](#)).

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

2.1. Newly triggered procedures

None

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

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

For further details, see also the adopted [PRAC recommendations on signals](#) under the corresponding month.

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of granuloma

EPITT 20046 – New signal

¹ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

² 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

Lead Member State(s): BE

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 granuloma was identified by the Danish Medicines Agency based on 99 cases retrieved from EudraVigilance and 53 cases retrieved from the Danish adverse effects database (Business Objects (Empirica)). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from post-marketing data and literature, PRAC agreed that further evaluation on the signal of granuloma is warranted.

Summary of recommendation(s)

- The MAH for Gardasil 9 (human papillomavirus 9-valent vaccine (recombinant, adsorbed)) and Gardasil (human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)) should submit to EMA, within 60 days, a cumulative review of the cases of granuloma, including an analysis of all case reports of the high level term (HLT) 'granulomatous and deep cutaneous inflammatory conditions', including the MedDRA preferred term (PT) 'nodule' as well as the relevant PTs that fall under the HLT 'skin and subcutaneous conditions NEC'. The cumulative review should be performed separately for the two vaccines, and should include data from clinical trials, scientific literature and post-marketing exposure. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) including relevant risk minimisation measures.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. [Abemaciclib – VERZENIOS \(CAP\) - EMEA/H/C/004302/SDA/004](#); [Palbociclib – IBRANCE \(CAP\) - EMEA/H/C/003853/SDA/005](#); [Ribociclib – KISQALI \(CAP\) - EMEA/H/C/004213/SDA/006](#)

Applicant(s): Eli Lilly Nederland B.V. (Verzenios), Pfizer Europe MA EEIG, Novartis Europharm Limited (Kisqali)

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of erythema multiforme

EPITT 19973 – Follow-up to October 2023³

³ Held 25 – 28 September 2023

Background

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

The MAHs replied to the request for information on the signal of erythema multiforme 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 MAHs, PRAC considered that a causal association between the under-assessment kinase inhibitors and erythema multiforme is at least a reasonable possibility, and that the product information should be updated to add as an undesirable effect with the frequency 'rare' for Verzenios (abemaciclib) and Kisqali (ribociclib), and as 'uncommon' for Ibrance (palbociclib).

Summary of recommendation(s)

- The MAHs for Ibrance (palbociclib), Kisqali (ribociclib) and Verzenios (abemaciclib) should submit to EMA, within 60 days, a variation to amend⁴ the product information.

4.3.2. [Elasomeran - SPIKEVAX \(CAP\) - EMEA/H/C/005791/SDA/131](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of postmenopausal haemorrhage

EPITT 20015 – Follow-up to November 2023⁵

Background

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

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

Discussion

Having considered the available evidence from literature and post-marketing data, as well as the response from the MAH, PRAC considered that the current evidence is insufficient to establish a causal relationship between Spikevax (elasomeran) and postmenopausal haemorrhage to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should continue to monitor postmenopausal haemorrhage through routine pharmacovigilance.

4.3.3. [Glucagon-like peptide-1 \(GLP-1\) receptor agonists: dulaglutide – TRULICITY \(CAP\) - EMEA/H/C/002825/SDA/015; exenatide – BYDUREON \(CAP\) - EMEA/H/C/002020/SDA/031, BYETTA \(CAP\) - EMEA/H/C/000698/SDA/051; insulin degludec, liraglutide – XULTOPHY \(CAP\) - EMEA/H/C/002647/SDA/003; liraglutide – SAXENDA \(CAP\) - EMEA/H/C/003780/SDA/021, VICTOZA \(CAP\) -](#)

⁴ Update of SmPC section 4.8. The package leaflet is updated accordingly.

⁵ Held 23 – 26 October 2023

EMA/H/C/001026/SDA/041; insulin glargine, lixisenatide – SULIQUA (CAP) -
EMA/H/C/004243/SDA/010; lixisenatide - LYXUMIA (CAP) -
EMA/H/C/002445/SDA/018; semaglutide – OZEMPIC (CAP) -
EMA/H/C/004174/SDA/009, RYBELSUS (CAP) - EMA/H/C/004953/SDA/014,
WEGOVY (CAP) - EMA/H/C/005422/SDA/008; tirzepatide – MOUNJARO (CAP) -
EMA/H/C/005620/SDA/006

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

PRAC Rapporteur: Mari Thorn

Scope: Signal of aspiration and pneumonia aspiration

EPITT 19974 – Follow-up to October 2023⁶

Background

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

The MAHs replied to the request for information on the signal of aspiration and pneumonia aspiration, and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and literature, as well as the responses from the MAHs, PRAC considered that the current evidence is insufficient to adopt a recommendation as per the causal relationship between GLP-1 receptor agonists (RAs) and aspiration and aspiration pneumonia.

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), for Trulicity (dulaglutide), and for Mounjaro (tirzepatide) should submit to EMA, within 60 days, their responses to the list of questions (LoQs) to discuss any recommendation on the appropriate time to stop GLP-1 RAs before a medical procedure requiring sedation or anaesthesia, on a specific timeframe for fasting and an appropriate medical procedure to confirm an empty stomach, as well as on an update of the product information (PI), if warranted based on these discussions. In addition, the MAHs for Mounjaro (tirzepatide), for Ozempic, Rybelsus and Wegovy products containing semaglutide, for Victoza and Saxenda products containing liraglutide, for Xultophy (insulin degludec, liraglutide) as well as for Byetta and Bydureon products containing exenatide, should further discuss and provide clarifications on some cases from the clinical trials that were excluded from the analysis. The MAH for Mounjaro (tirzepatide) should also provide a literature review on aspiration, pneumonia aspiration, anaesthetic complication pulmonary and tirzepatide/GLP-1 RAs, including a discussion on the recent case of tirzepatide use and emesis described by *Weber et al*⁷. Based on the available data, the MAH for Trulicity (dulaglutide) should also provide evidence if a suitable time-window for treatment discontinuation of dulaglutide

⁶ Held 25 – 28 September 2023

⁷ Weber M, Siddarthan I, Mack PF. Clinically significant emesis in a patient taking a long-acting GLP-1 receptor agonist for weight loss. *Br J Anaesth.* 2023 Aug;131(2):e37-e39

can be identified that may be sufficient to ensure complete gastric emptying, and submit the protocol of study H9X-EW-GBDM (GBDM) and discuss the result of the study, as well as provide a discussion on an update of the PI if warranted based on these discussions. Furthermore, the MAH for Lyxumia (lixisenatide) and for Suliqua (insulin glargine, lixisenatide) should discuss further specific cases and provide clarifications on the searches of MedDRA preferred terms (PTs) in the global pharmacovigilance database, on the literature searches, on the reference to publication of *Bailey et al 2013*⁸. Finally, the MAH for Byetta and Bydureon products containing exenatide should provide also clarifications and narratives for specific cases, and on the literature search including the used criteria.

- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.4. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/068

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Signal of postmenopausal haemorrhage

EPITT 19989 – Follow-up to November 2023⁹

Background

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

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

Discussion

Having considered the available evidence from literature and post-marketing data, as well as the response from the MAH, PRAC considered that the current evidence is insufficient to establish a causal relationship between Comirnaty (tozinameran) and postmenopausal haemorrhage to further warrant an update to the product information and/or risk management plan at present.

Summary of recommendation(s)

- The MAH for Comirnaty (tozinameran) should continue to monitor postmenopausal haemorrhage through routine pharmacovigilance.

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

None

⁸ Bailey CJ, Berria R, Stager W, et. al. Consistent reduction of postprandial glucagon and insulin by lixisenatide in the GetGoal clinical trial programme. *Diabetologia*. 2013 Sep;56(Suppl. 1):S403

⁹ Held 23 – 26 October 2023

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. Apadamtase alfa - (CAP MAA) - EMEA/H/C/006198, Orphan

Applicant: Takeda Manufacturing Austria AG

Scope (pre D-180 phase): treatment of congenital thrombotic thrombocytopenic purpura (cTTP) due to ADAMTS13 deficiency

5.1.2. Beremagene geperpavec - (CAP MAA) - EMEA/H/C/006330, PRIME, Orphan

Applicant: Krystal Biotech Netherlands B.V., ATMP

Scope (pre D-120 phase): treatment of patients from birth with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene

5.1.3. Dasiglucagon - (CAP MAA) - EMEA/H/C/006214

Scope (pre D-180 phase): Treatment of severe hypoglycaemia in patients with diabetes

5.1.4. Fidanacogene elaparvovec - (CAP MAA) - EMEA/H/C/004774, PRIME

ATMP

Scope (pre D-180 phase): Treatment of severe and moderately severe haemophilia B

5.1.5. RdESAT-6, rCFP-10 - (CAP MAA) - EMEA/H/C/006177

Scope (pre D-180 phase): Diagnosis of infection with *Mycobacterium tuberculosis*

5.1.6. Zolbetuximab - (CAP MAA) - EMEA/H/C/005868, Orphan

Applicant: Astellas Pharma Europe B.V.

Scope (pre D-180 phase): Treatment of locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

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. Mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/II/0170/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Karin Erneholm

Scope: C.I.6.a: Extension of indication to include paediatric patients (3 months to 18 years of age) for hepatic and cardiac transplants and to extend the indication for renal transplants for paediatric patients starting from 3 months, based on pharmacokinetic data, published literature and the Roche Global Safety Database. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The package leaflet is updated accordingly. Type IB (C.I.z): To update section 4.2 of the SmPC for the CellCept 500 mg tablets formulation in order to be in line with the other three CellCept formulations. And for alignment with the current QRD guidance, the package leaflet was updated to cross reference section 2 in section 6 for sodium content. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and bring the product information in line with the latest QRD template version 10.3

Background

CHMP is evaluating a type II variation for Cellcept, a centrally authorised product containing mycophenolate mofetil, to extend the indication in order to include paediatric patients (3 months to 18 years of age) for hepatic and cardiac transplants and for renal transplants for paediatric patients starting from 3 months, as well as to update relevant sections of the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure.

Summary of advice

- PRAC did not agree with the MAH's justification for not submitting an RMP and concluded that an updated RMP is warranted, considering the new indication and the differences in frequency of certain events between paediatric HTx and LTx patients in comparison to adult groups or to Rx patients, indicating that the current safety knowledge cannot be extrapolated from the currently approved indications and age groups. Moreover, PRAC pointed out that there are still uncertainties regarding long term safety issues in this age group, such as growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development.

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.

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.

6.1.1. Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202307

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Saphnelo, a centrally authorised medicine containing anifrolumab 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 Saphnelo (anifrolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add arthralgia with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁰.
- In the next PSUR, the MAH should continue to monitor and discuss fatal cases of serious infections, including a discussion on the update of 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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the EURD list will be updated accordingly.

6.1.2. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202308

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Blenrep, a centrally authorised medicine containing belantamab mafodotin 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 Blenrep (belantamab mafodotin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'hepatitis B virus reactivation' as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹¹.

¹⁰ 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.

¹¹ 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.

- In the next PSUR, the MAH should provide a cumulative review of cases of nodular regenerative hyperplasia, including a causality assessment and a discussion on the need for updating the product information. The MAH should also provide a review of cases of tumour lysis syndrome (TLS) and discuss whether there is a need for an update of the product information. Furthermore, the MAH should provide a review of cases of hepatitis B reactivation cases reported in clinical trials, including a proposal for a frequency for this event, in order to update 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.

6.1.3. [Dengue tetravalent vaccine \(live, attenuated\) - DENGUE TETRAVALENT VACCINE \(Art 58¹²\) - EMEA/H/W/005362/PSUV/0011](#)

Applicant: Takeda GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUR procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Dengue Tetravalent Vaccine (live, attenuated) Takeda, a medicine authorised in accordance with Article 58 of Regulation (EC) No 726/2004 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 Dengue Tetravalent Vaccine (live, attenuated) Takeda in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on vaccine viremia to make healthcare professionals aware of the possibility of positive dengue diagnostic tests after vaccination. Therefore, the current terms of the marketing authorisation(s) should be varied¹³.

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.

6.1.4. [Darolutamide - NUBEQA \(CAP\) - PSUSA/00010843/202307](#)

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

¹² 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)

¹³ Update of SmPC section 4.8. 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 Nubeqa, a centrally authorised medicine containing darolutamide 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 Nubeqa (darolutamide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on hepatotoxicity and also to amend the description of liver function tests. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁴.

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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.5. Dengue tetravalent vaccine¹⁵ (live, attenuated) - QDENGGA (CAP) - PSUSA/00011034/202308

Applicant: Takeda GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Qdenga, a centrally authorised medicine containing dengue tetravalent vaccine (live, attenuated) 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 Qdenga (dengue tetravalent vaccine (live, attenuated)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on vaccine viremia to make healthcare professionals aware of the possibility of positive dengue diagnostic tests after vaccination. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁶.

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.

¹⁴ 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.

¹⁵ Dengue virus, serotype 2, expressing Dengue virus, serotype 1, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 3, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 4, surface proteins, live, attenuated, Dengue virus, serotype 2, live, attenuated

¹⁶ Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

6.1.6. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202308

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Ibrance, a centrally authorised medicine containing palbociclib 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 Ibrance (palbociclib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add blood creatinine increased as an undesirable effect with a frequency 'common'. Moreover, the product information should be updated to reflect the drug-drug interaction between palbociclib and statins. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should provide cumulative reviews of cases of pancytopenia, gastrointestinal inflammatory disorders (NES) and of skin pigmentation disorders, including data from clinical trials, spontaneous reports and literature and discuss the need for update of the product information, as 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.

6.1.7. Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202308

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Regkirona, a centrally authorised medicine containing regdanvimab 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 Regkirona (regdanvimab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

¹⁷ Update of SmPC sections 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

- In the next RMP update, the MAH should remove the targeted follow-up questionnaire for lack of efficacy due to emerging variants.

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. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.8. [Smallpox and monkeypox vaccine \(Live Modified Vaccinia Virus Ankara\) - IMVANEX \(CAP\) - PSUSA/00010119/202307](#)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Imvanex, a centrally authorised medicine containing smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara) 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 Imvanex (smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara)) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anxiety-related reactions as a warning and to add acute peripheral facial paralysis (Bell's palsy) as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁸.
- In the next PSUR, the MAH should include a cumulative analysis of all safety concerns, including data from clinical trials and post-marketing, and a description of the missing 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.

6.1.9. [Upadacitinib - RINVOQ \(CAP\) - PSUSA/00010823/202308](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Petar Mas

Scope: Evaluation of a PSUSA procedure

Background

¹⁸ 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.

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Rinvoq, a centrally authorised medicine containing upadacitinib 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 Rinvoq (upadacitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add vertigo and dizziness as undesirable effects with a frequency 'common', and consequently to amend the warning on the ability to drive and use machines. In addition, the additional risk minimisation measures (Guide for healthcare professionals and Patient card) should be updated to strengthen the warning regarding previous medical history of tuberculosis or exposure to tuberculosis as an important risk factor in developing tuberculosis following treatment with upadacitinib. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the MAH should provide a cumulative review of cases reported under standardised MedDRA query (SMQ) Hypertension (broad), including a causality assessment and discuss the need for an update of 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.

6.1.10. Voxelotor - OXBRYTA (CAP) - PSUSA/00010983/202308

Applicant: Pfizer Europe Ma EEIG

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

Background

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Oxbryta, a centrally authorised medicine containing voxelotor 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 Oxbryta (voxelotor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pruritus and angioedema as undesirable effects with frequency 'common' and 'not known' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²⁰.
- In the next PSUR, the MAH should provide a cumulative review of the most relevant cases with documented increased occurrence of vaso-occlusive disorder in the period

¹⁹ Update of SmPC sections 4.7 and 4.8 and Annex II-D. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

²⁰ Update of SmPC section XX. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

after treatment initiation when compared to the patient medical history of vaso-occlusive disorder before voxelotor, including data from clinical trials, post-marketing setting and literature. The MAH should propose risk minimisation measures and discuss how the results impact the benefit/risk balance of voxelotor in the approved indication, as 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.

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

See also Annex I 16.2.

6.2.1. Leuprorelin²¹ - CAMCEVI (CAP); NAP - PSUSA/00010877/202307

Applicant: Accord Healthcare S.L.U. (Camcevi), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Leuprorelin acetate is a synthetic gonadotropin releasing hormone (GnRH) and it is indicated for the treatment of endometriosis, breast cancer, advanced hormone-dependent prostate cancer, central precocious puberty, female infertility, uterus myomatosis, uterine fibrosis, subject to certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Camcevi, a centrally authorised medicine containing leuprorelin, and nationally authorised medicines containing leuprorelin (depot formulations) 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 leuprorelin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add fatty liver to the existing warning on metabolic changes, as well as to add severe cutaneous adverse reactions (SCARs) as a warning and Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) as undesirable effects with a frequency 'not known'. PRAC also considered that a causal association of leuprorelin with erythema multiforme and toxic skin eruption is at least a reasonable possibility, and that the product information should be updated to add these undesirable effects with the frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied ²².

²¹ Depot formulation(s) only

²² 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.

- In the next PSUR, the MAH(s) should provide a cumulative review of cases of cerebral venous sinus thrombosis.

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. Anastrozole (NAP) - PSUSA/00000210/202308

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

Background

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor (NSAI) and it is indicated for the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women, adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women and for adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing anastrozole 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 anastrozole-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 MAH(s) should further monitor cases of tendonitis, tendosynovitis and tendon rupture, as well as of lichenoid eruption and erythema nodosum with particular attention to cases which are confirmed by skin biopsy, including causality assessments and discuss if an update of the product information is warranted. The MAH(s) should also provide cumulative reviews of cases of dry eye, eye disorders and of memory impairment and related terms with the use of anastrozole, including data from clinical trials, observational studies, literature and spontaneous reports. The MAH(s) should provide a discussion on the causality and biological mechanism, as well as on the need for updating 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.

6.3.2. Atorvastatin, ezetimibe (NAP) – PSUSA/00010385/202307

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Atorvastatin is a synthetic lipid-lowering agent and a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, and ezetimibe is a lipid modifying agent which selectively inhibits the intestinal absorption of cholesterol and related plant sterols. As a combination atorvastatin/ezetimibe, it is indicated for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH) and for prevention of cardiovascular disease.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing atorvastatin/ezetimibe 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 atorvastatin/ezetimibe-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 MAH(s) for atorvastatin/ezetimibe-containing medicinal products should provide cumulative reviews of cases of immune-mediated necrotizing myopathy (IMNM) and review the issue of genetic polymorphisms for atorvastatin. In addition, the MAH should continue to closely monitor cases of bullous pemphigoid, lichen planus and cutaneous vasculitis/vasculitis and new information should be presented in the next PSUR.

The frequency of PSUR submission should be revised from five-yearly to seven-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.

6.3.3. Paracetamol, tramadol (NAP) - PSUSA/00002310/202308

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

Background

Paracetamol is para-aminophenol derivative with analgesic and antipyretic properties and tramadol is an opioid. In combination paracetamol/tramadol, it is indicated for oral use for the symptomatic treatment of moderate to severe pain.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing paracetamol/tramadol 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 paracetamol/tramadol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, in view of available data on drug abuse and dependence (opioid use disorder) from the literature and recent assessments of PSUSA procedures for other opioids, the existing warning on drug dependence and potential for abuse should be further strengthened. In addition, amendments to the package leaflet are warranted to highlight the potential serious consequences of accidental ingestion and the importance of appropriate storage. The product information should also be updated to reflect the drug-drug interaction with gabapentinoids. Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH(s) of the paracetamol/tramadol-containing products should provide further data on risk of toxic leukoencephalopathy in a context of tramadol overdose, on disseminated intravascular coagulation in a context of paracetamol overdose. Furthermore, the MAH(s) should provide further reviews on cases of pancreatitis and/or sphincter of Oddi dysfunction, QT prolongation, hyponatraemia/syndrome of inappropriate antidiuretic hormone (ADH) release (SIADH), opioid-induced hyperalgesia (OIH) and allodynia, and opioid dependence, including abuse, misuse and withdrawal syndrome as part of the PSUR safety concerns. Based on this data, the MAH(s) should discuss whether there is a need for an update of the product information, as 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.

6.3.4. Quetiapine (NAP) - PSUSA/00002589/202307

Applicant(s): various

PRAC Lead: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Quetiapine is an atypical antipsychotic indicated for the treatment of schizophrenia, treatment of bipolar disorder and for the add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy, subject to certain conditions.

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

²³ Update of SmPC sections 4.2, 4.4, 4.5, 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 quetiapine-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 serotonin syndrome following the concomitant use of quetiapine and other serotonergic agents. Therefore, the current terms of the marketing authorisation(s) should be varied²⁴.
- In the next PSUR, the MAH(s) for quetiapine-containing products should re-classify 'suicide and suicidality' from important potential risk to important identified risk in the PSUR list of safety concerns. In addition, the MAH brand leader for quetiapine-containing products should continue to monitor cases of abuse and misuse of quetiapine and of off-label use, as well as discuss the effectiveness and usefulness of the additional risk minimisation measures in place for quetiapine-containing products.

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.

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Burosumab - CRYSVITA (CAP) - EMEA/H/C/004275/LEG 008

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of a safety review on cases craniosynostosis as per the conclusions from PSUSA/00010669/202302 adopted by PRAC in October 2023.

Background

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit further data on craniosynostosis. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the available data and the Rapporteur's assessment, PRAC agreed that, currently, there is insufficient evidence to establish a causal relationship between burosumab and craniosynostosis; however, PRAC considered warranted to update the product information to amend the warning on ectopic mineralisation in order to add craniosynostosis and to monitor children on treatment for signs of craniosynostosis.
- The MAH should submit to EMA, within 60 days, a variation to amend²⁵ the product information.

²⁴ Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position.

²⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See also Annex I 16.5.

6.5.1. Isatuximab - SARCLISA (CAP) - EMEA/H/C/004977/II/0027

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.8 of the SmPC in order to add 'thrombocytopenia' and 'anaemia' to the list of adverse drug reactions (ADRs) and to amend the frequency of all remaining ADRs with their appropriate frequencies, following PRAC request in the outcome of the PSUSA procedure PSUSA/00010851/202303

Background

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH to submit a variation to update the product information in order to add 'thrombocytopenia' and 'anaemia' to the list of ADRs and to amend the frequency of all remaining ADRs with their appropriate frequencies. PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of CHMP, responsible for adopting an opinion on this variation.

Summary of recommendation(s)

- Based on the available data, the Rapporteur's assessment and the MAH's responses, PRAC agreed that the product information should be amended to include thrombocytopenia, anaemia and lymphopenia as undesirable effects in the tabulated lists of adverse reactions under MedDRA System Organ Class (SOC) 'blood and lymphatic system disorders', with their respective frequencies and to update the incidence of haematological abnormalities to include all events, regardless of action taken.

6.6. Expedited summary safety reviews²⁶

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)²⁷

See Annex I 17.1.

²⁶ 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

²⁷ In accordance with Article 107n of Directive 2001/83/EC

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)²⁸

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)²⁹

See Annex I 17.3.

7.4. Results of PASS non-imposed in the marketing authorisation(s)³⁰

See Annex I 17.4.

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.

²⁸ 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

²⁹ In accordance with Article 107p-q of Directive 2001/83/EC

³⁰ 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

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. Other requests

11.1.1. Xylitol, magnesium sulfate heptahydrate, potassium chloride, procaine hydrochloride (NAP)

PRAC Lead: Jan Neuhauser

Scope: PRAC consultation on the evaluation of an initial marketing authorisation application under the decentralised procedure for the cardioplegic solution containing xylitol, magnesium sulfate heptahydrate, potassium chloride, procaine hydrochloride in order to consider the need for additional pharmacovigilance activities to assess the effectiveness of proposed additional risk minimisation measures on request of Austria

Background

In the context of the evaluation of an initial marketing authorisation application under the decentralised procedure for the cardioplegic solution containing xylitol, magnesium sulfate heptahydrate, potassium chloride, procaine hydrochloride, Austria requested PRAC advice on its assessment.

11.1.2. Valproate³¹ (NAP) - NL/H/xxxx/WS/794

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

PRAC Lead: Liana Martirosyan

Scope: PRAC consultation on a work sharing variation, with focus on the assessment of the protocol for the (category 3) qualitative study proposed by the Consortium of MAHs to investigate barriers and reasons why certain measures of the pregnancy prevention program (PPP) are not always followed in clinical practice while knowledge on these aspects seems sufficient, as indicated by the final results of a category 1 study EUPAS34465: a survey among healthcare professionals (HCP) and patients to assess their knowledge and behaviour with respect to the new (2018) risk minimization measures (RMM) for valproate use in Europe.

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.

Following the PRAC recommendation on valproate-containing medicinal products in the context of the assessment of the results of study EUPAS34465 the Consortium of MAHs submitted to the national competent authorities the protocol for the category 3 (qualitative) study above noted.

The Consortium of MAHs proposed a qualitative study using individual interviews with patients and individual interviews and focus groups with different types of HCPs.

In the context of this work sharing variation procedure, the Netherlands requested PRAC advice on its assessment.

Summary of advice

Based on the review of the available information, PRAC agreed, in principle, with the assessment of the reference member state, with different suggestions. The proposed choice of countries should be expanded to ensure an adequate representation of all European regions to capture not only different healthcare systems, prescribing or dispensing attitudes, but also ways of implementing RMMs and cultural diversity in the EU. In addition, the number

³¹ Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium

of (additional) countries should be balanced for an adequate representation of all EU (different) regions, without triggering challenges at the time of data analyses.

The study will be conducted until data saturation is reached in each country for each category of participants, patients and HCPs, separately. Although the exact sample size will be driven by data saturation and the MAH should clearly describe in the protocol how this is reached, while a minimum number should be specified for each subgroup of HCPs (e.g. neurologist, psychiatrist, GP, etc).

PRAC supported that only HCPs should be included in the focus groups, as proposed by the MAH. Their collaborative relationships in daily practice and multidisciplinary care of patients receiving valproate are crucial elements which might reveal valid points on insufficient effectiveness of the pregnancy prevention programme (PPP) during the discussions. An experienced moderator, posing neutral questions, would also be a key factor to ensure fruitful discussions.

Having considered the proposed questions in the interview guides, PRAC agreed that subjective, judgemental, speculative or leading questions (throughout the HCP guides) should be avoided; more open-ended, positive or neutral questions should be preferred, with the aim to identify any barrier impacting PPP effectiveness. In addition, some questions could be shortened or simplified, particularly those for patients, while consideration could also be given to reduce the number of questions.

11.2. Safety related variations of the marketing authorisation

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

The Chair welcomed Marjetka Plementas, as the new alternate for Slovenia.

12.1.2. Vote by proxy

None

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

The EMA Secretariat provided PRAC with an update on the new SARS-CoV-2 variants and COVID-19 vaccines and adverse events of special interest. An update on the proposed timeline to harmonise and align better with the launch of COVID-19 and flu vaccines as presented in the WHO/ICMRA workshop on 26-27 February 2024 was also provided to PRAC along with an update on alternative lists of agents used for chemical or bioterrorism and the WHO guidance, as well as on Monkeypox and smallpox.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version March 2024, reflecting the 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 March 2024, the updated EURD list was adopted by CHMP and CMDh at their March 2024 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

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

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

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

None

12.13.2. EudraVigilance annual report 2023

The EMA Secretariat presented the annual report related to EudraVigilance activities on the reporting of adverse drug reactions as well as an analysis on signal detection and signal outcomes for the year 2023.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

12.20.1. GVP Module XVI (Rev.3) on Risk Minimisation Measures: post-public consultation draft Addendum II on Methods for Effectiveness Evaluation

PRAC lead: Liana Martirosyan

The EMA Secretariat presented the updated GVP M XVI (Rev.3) Addendum II on methods for risk minimisation measures (RMMs) effectiveness evaluation following the public consultation launched in 2021. For background information, see [PRAC minutes June 2021](#). PRAC was informed on the main changes and the comments received, and members were invited to send their comments in writing until 19 March 2024. Subsequent steps include further consultation at the level of other committees, interaction with the EC and adoption by HMA's EU-POG and the EMA HoA, aiming of final document publication by Q2 2024.

Post meeting note: GVP M XVI (Rev.3) Addendum II (Methods for effectiveness evaluation) was adopted by PRAC via written procedure on 9 April 2024.

12.20.2. Joint Heads of Medicines Agencies (HMA)/European Medicines Agency (EMA) Multistakeholder workshop on Patient Registries

The EMA Secretariat presented the main outcomes of the workshop [Joint Heads of Medicines Agencies \(HMA\)/European Medicines Agency \(EMA\) Multistakeholder workshop on Patient Registries](#) held on 12-13 February 2024. For background information, see [PRAC Minutes October 2023](#). A detailed report is currently under preparation based on the rich and useful breakout discussions, while members can visit EMA's webpage to watch the recording and have access to the presentations. PRAC noted the information.

12.21. Others

12.21.1. Amendments to the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities - update

The European Commission (EC) representative to PRAC presented to the committee an update on the amendments to the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities. For background information, see [PRAC Minutes March 2021](#). As part of the pharmaceutical Strategy for Europe, PRAC was informed on the main issues identified and the proposed possible solutions as well as the timelines for comments and adoption that it is expected by the second quarter of 2024. For more information, see [Performance of pharmacovigilance activities for human medicines \(update of Implementing Regulation \(EU\) 520/2012\) \(europa.eu\)](#). PRAC noted the information and

was invited to provide any comments during this public consultation phase via the dedicated route: [Have your say - Public Consultations and Feedback \(europa.eu\)](https://european-council.europa.eu/media/en/multi-media-centre/actions/consultations/details/initiative/163432/2024).

13. Any other business

None

14. Annex I – Signals assessment and prioritisation³²

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 timetables³³.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Acetazolamide (NAP)

Applicant: various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pulmonary oedemas

EPITT 20050 – New signal

Lead Member State(s): SE

14.1.2. Bumetanide (NAP)

Applicant: various

PRAC Rapporteur: Mari Thörn

Scope: Signal of toxic epidermal necrolysis

EPITT 20033 – New signal

Lead Member State(s): SE

14.1.3. Dupilumab – DUPIXENT (CAP)

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of thrombocytopenia

EPITT 20054 – New signal

³² 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

³³ 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

Lead Member State(s): FI

14.1.4. Entrectinib – ROZLYTREK (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Signal of myocarditis

EPITT 20059 – New signal

Lead Member State(s): NL

14.1.5. Epcoritamab – TEPKINLY (CAP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Signal of progressive multifocal leukoencephalopathy

EPITT 20056 – New signal

Lead Member State(s): ES

14.1.6. Glofitamab – COLUMVI (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Signal of immune effector cell-associated neurotoxicity syndrome

EPITT 20058 – New signal

Lead Member State(s): CZ

14.2. New signals detected from other sources

None

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. Dasatinib - (CAP MAA) - EMEA/H/C/006251

Scope (pre D-180 phase): Treatment of chronic myelogenous leukaemia (CML)

15.1.2. Dimethyl fumarate - (CAP MAA) - EMEA/H/C/006471

Scope: Treatment of multiple sclerosis

15.1.3. Dimethyl fumarate - (CAP MAA) - EMEA/H/C/006500

Scope: Treatment of multiple sclerosis

15.1.4. Dimethyl fumarate - EMEA/H/C/006397

Scope: Treatment of multiple sclerosis

15.1.5. Rituximab - (CAP MAA) - EMEA/H/C/006224

Scope (pre D-180 phase): Treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis

15.1.6. Ustekinumab - (CAP MAA) - EMEA/H/C/005918

Scope (pre D-180 phase): Treatment of adult patients with moderately to severely active Crohn's disease, plaque psoriasis, paediatric plaque psoriasis and psoriasis arthritis (PA)

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. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/II/0060

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 4.2 after approval of adapted COVID-19 vaccine by new strain, Omicron XBB.1.5

15.2.2. Romiplostim - NPLATE (CAP) - EMEA/H/C/000942/II/0091

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of an updated RMP version 22 in order to include the latest safety information collected until 31 July 2023 (data lock point). The main change consists of removing the neutralising antibodies that cross-react with endogenous thrombopoietin (eTPO)

15.2.3. Sacituzumab govitecan - TRODELVY (CAP) - EMEA/H/C/005182/II/0031

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Bianca Mulder

Scope: Submission of an updated RMP version 3.1 in order to propose the removal of some safety concerns and the extension of remaining study milestones to date for Category 3 study IMMU-132-15

15.2.4. 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. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/X/0036/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Mari Thorn

Scope: Extension application to introduce a new strength, 80 mg [0.8 ml (100 mg/ml)] solution for injection, grouped with various quality variations.

The RMP (version 6.0) is updated in accordance

15.3.2. Alectinib - ALECENSA (CAP) - EMEA/H/C/004164/II/0047

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Extension of indication to include the use of Alecensa as monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) as adjuvant treatment following tumour resection, based on final results from study BO40336 (ALINA): a randomised, active controlled, multicentre, open-label, Phase III study designed to evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting in patients with completely resected Stage IB (tumors 4 cm) to Stage IIIA ALKpositive NSCLC. 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 4.0 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 and to introduce editorial changes to the product information. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.3. Amivantamab - RYBREVANT (CAP) - EMEA/H/C/005454/II/0011

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI) for RYBREVANT, based on the final results from study 61186372NSC3002 (MARIPOSA 2); this is a randomised, open label, multicentre Phase 3 study that compares efficacy and safety of amivantamab in combination with carboplatin and pemetrexed (ACP) with carboplatin and pemetrexed (CP). The primary objective of the MARIPOSA 2 study is to compare efficacy, as demonstrated by PFS, in participants treated with ACP versus CP alone. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.6 and 9 of the SmPC are updated. The package leaflet is updated in accordance. Version 3.2 of the EU RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) is requesting an additional year of market protection

15.3.4. Andexanet alfa - ONDEXXYA (CAP) - EMEA/H/C/004108/II/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information based on the final results from study 18-513 (ANNEXA-I), listed as a specific obligation in the Annex II; this is a phase 4 randomised controlled trial to investigate the efficacy and safety of andexanet alfa versus usual care in patients with acute intracranial haemorrhage taking apixaban, rivaroxaban or edoxaban. Consequently, the MAH proposes a switch from conditional marketing authorisation to full marketing authorisation. The Annex II and package leaflet are updated accordingly. The updated RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring it in line with the latest QRD template version 10.3

15.3.5. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/II/0044/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Monica Martinez Redondo

Scope: A grouped application of a Type II Variation with two Type IA Variations, as follows: Type II (C.I.6.a): Extension of indication to include the treatment of moderate to severe chronic plaque psoriasis in children and adolescents from the age of 6 years who have a contraindication, have an inadequate response, or are intolerant to at least one other systemic therapy or phototherapy for OTEZLA, based on final results from study CC-10004-PPSO-003 as well as results from studies CC-10004-PPSO-001 and CC-10004-PPSO-004. CC-10004-PPSO-003 is a phase 3, multicentre, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of apremilast (CC-10004) in paediatric subjects from 6 through 17 years of age with moderate to severe plaque psoriasis. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated.

The package leaflet and labelling are updated in accordance. Version 15.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial and formatting changes to the product information and to update the list of local representatives in the package leaflet.

2 Type IA (B.II.e.5.a.1): Update of sections 6.5 and 8 of the SmPC to introduce two new pack sizes within approved range as a result of the indication update (27 film-coated tablets (4 x 10 mg, 23 x 20 mg) and 14 film-coated tablets (14 x 20mg), in a pack size of 56 tablets)

15.3.6. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/II/0052

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include treatment of eosinophilic granulomatosis with polyangiitis (EGPA) for Fasenra, based on results from study D3253C00001 (Mandara); this was a randomised, double-blind, multicentre, parallel group, active-controlled, non-inferiority study that evaluated the efficacy and safety of benralizumab compared with mepolizumab in treatment of patients with EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 6.1 of the RMP has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.7. Budesonide, formoterol fumarate dihydrate - BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP) - EMEA/H/C/004882/II/0012/G

Applicant: Teva Pharma B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) To replace the multidose dry powder inhaler to be used for the delivery of a combination of Budesonide/Formoterol fumarate dihydrate inhalation powder, as well as detect, record, store and transfer inhaler usage information to a mobile application (App); the inhaler is an integrated part of the primary packaging of the medicinal product; 2) To change the name of the medicinal product; 3) To update sections 4.2 and 4.4 of the SmPC to reorganise the flow of information within these sections (as approved for DuoResp Spiromax EMEA/H/C/002348), following assessment of the same change for the reference product Symbicort Turbohaler; 4) other quality variations

15.3.8. Cariprazine - REAGILA (CAP) - EMEA/H/C/002770/X/0033

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension application to introduce a new pharmaceutical form (orodispersible tablets). The RMP (version 3.0) is updated in accordance

15.3.9. Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0015

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on a comprehensive analysis of the results from the drug pregnancy registry cohort (PDC study GV44373), listed as a category 3 PASS in the RMP, as well as data from clinical studies and post-marketing surveillance. The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to update the list of local representatives in the package leaflet

15.3.10. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/X/0080/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Extension application to introduce a new pharmaceutical form (granules in capsules for opening) associated with new strengths (20, 50 and 150 mg), grouped with a type II variation (C.I.6.a) to include the treatment of paediatric patients with relapsed or refractory, systemic ALK-positive ALCL or unresectable, recurrent, or refractory ALK-positive IMT to change the lower end of the age range from ≥ 6 years to ≥ 1 year for Xalkori following the assessment of II/0072 based on final results from study ADVL0912. 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 9.1 of the RMP has also been submitted

15.3.11. Dengue tetravalent vaccine³⁴ (live, attenuated) - DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED) TAKEDA (Art 58³⁵) - EMEA/H/W/005362/WS2593/0012; Dengue tetravalent vaccine (live, attenuated) - QDENG A (CAP) - EMEA/H/C/005155/WS2593/0013

Applicant: Takeda GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Update of section 4.5 of the SmPC in order to add co-administration information with HPV vaccine based on final results from study DEN-308 listed as a category 3 study in the RMP (MEA003/MEA004); this is a Phase 3, open-label, randomised trial to investigate the immunogenicity and safety of the co-administration of a subcutaneous dengue tetravalent vaccine (live, attenuated) (TDV) and an intramuscular recombinant 9-valent human papillomavirus (9vHPV) vaccine in subjects aged ≥ 9 to < 15 years in an endemic country for dengue; the package leaflet is updated accordingly. The RMP version 1.1 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes and to update the text on PSUR submissions in Annex II for Dengue tetravalent vaccine

³⁴ Dengue virus, serotype 2, expressing Dengue virus, serotype 1, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 3, surface proteins, live, attenuated, Dengue virus, serotype 2, expressing Dengue virus, serotype 4, surface proteins, live, attenuated, Dengue virus, serotype 2, live, attenuated

³⁵ 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)

15.3.12. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0116

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of paediatric patients from 6 kg to less than 25 kg for Triumeq dispersible tablets, based on PK, safety, and efficacy data observed in the final results of study 205860 (IMPAACT 2019), further supported by extrapolation to data generated in adults and additional data in paediatric patients with the single entities. IMPAACT 2019 is a Phase 1/2 open-label, multicentre, multiple dose study of dolutegravir/lamivudine/abacavir fixed dose combination tablets in treatment-experienced and treatment-naïve HIV-1-infected children less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 22.0 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the product information

15.3.13. Dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/II/0057/G

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Nathalie Gault

Scope: Grouped application comprising two type II variations as follows:

C.I.13: Submission of the final report from study 201636 (SWORD 1) listed as a category 3 study in the RMP. This is a phase III, randomised, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus rilpivirine from current INI-, NNRTI-, or product information-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed.

C.I.13: Submission of the final report from study 201637 (SWORD 2) listed as a category 3 study in the RMP. This is a phase III, randomised, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus rilpivirine from current INI-, NNRTI-, or product information-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed. The RMP version 7.0 has also been submitted

15.3.14. Durvalumab - IMFINZI (CAP) - EMEA/H/C/004771/II/0064

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, for the treatment of adults with resectable (tumours \geq 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements for IMFINZI, based on the interim results from study D9106C00001 (AEGEAN); this is a Phase III, double-blind, placebo-controlled, multicentre international study of neoadjuvant/adjunct durvalumab for the treatment of patients with resectable stages II and III non-small cell lung cancer. 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 11 of the RMP has also been submitted

15.3.15. Efgartigimod alfa - VYVGART (CAP) - EMEA/H/C/005849/II/0014, Orphan

Applicant: Argenx

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.4 of the SmPC in order to amend an existing warning on infusion reactions and hypersensitivity reactions, and update of section 5.1 of the SmPC to update the mechanism of action of efgartigimod in relation to albumin; based on final results from study ARGX-113-1705 listed a category 3 study in the RMP. This is a long-term, single-arm, open-label, multicentre, phase 3 follow-on study of ARGX-113-1704 to evaluate the safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalised muscle weakness. The RMP version 2.2 has also been submitted

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

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 (EMBARK); 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

15.3.17. Faricimab - VABYSMO (CAP) - EMEA/H/C/005642/II/0005

Applicant: Roche Registration GmbH

PRAC Rapporteur: Carla Torre

Scope: Extension of indication to include treatment of adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) for Vabysmo, based on results from the two phase 3 studies: GR41984 (BALATON) in patients with branch retinal vein occlusion (BRVO) and GR41986 (COMINO) in patients with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). These are global, multicentre, randomised, double-masked, active comparator-controlled, parallel-group, 2-part studies evaluating the efficacy, safety, and PK of faricimab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The package leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information

15.3.18. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0022/G, Orphan

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: A grouped application comprised of three Type II variations, as follows:

C.I.4: Update of sections 4.4 and 4.8 of the SmPC in order to modify the list of adverse drug reactions based on a revised safety ADR methodology for Dravet and Lennox-Gastaut syndromes, which includes pooled analyses encompassing studies ZX008-1503 and ZX008-1601 cohort B. The package leaflet is updated accordingly.

C.I.4: Update of section 5.1 of the SmPC in order to update clinical efficacy information for Dravet syndrome based on final results from study ZX008-1503 listed as a category 3 study in the RMP. This is an open-label extension trial to assess the long-term safety of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome.

C.I.4: Update of section 5.1 of the SmPC in order to update clinical efficacy information for Lennox-Gastaut syndrome based on final results from study ZX008-1601 Part 1 cohort B and interim results for study ZX008-1601 Part 2 cohort B. Study 1601 Part 1 was an international, randomised, double-blind, parallel-group, placebo-controlled study in subjects with LGS 2 to 35 years of age, while study 1601 Part 2 is a long-term, open-label, flexible-dose extension for subjects who completed study 1601 Part 1.

The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the product information, including to section 4.2 of the SmPC

15.3.19. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0037

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Extension of indication to include treatment of mixed hyperlipidaemia in adult patients while on a treatment with pravastatin 40 mg monotherapy or on another moderate-intensity statin regimen for PRAVAFENIX, based on final results from the non-interventional PASS: POSE (Pravafenix Observational Study in Europe); this is a European, observational, three-year cohort comparative study on the safety of the fixed dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix) versus statin alone in real clinical practice. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

15.3.20. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/II/0031/G

Applicant: Galapagos N.V.

PRAC Rapporteur: Petar Mas

Scope: Grouped application comprising two variations as follows:

Type II (C.I.4): Update of sections 4.8 and 5.1 of the SmPC to update the safety mean duration exposure and efficacy information based on final results (up to Week 432) from study GLPG0634-CL-205 (DARWIN 3) listed as a category 3 study in the RMP (MEA/009); this is a phase II, open-label, long-term follow-up safety and efficacy study to evaluate the long-term safety and tolerability of filgotinib for the treatment of Rheumatoid Arthritis in patients who received treatment in their parent studies. The RMP version 6.1 has also been submitted.

Type IA (A.6): To change the ATC code for Janus-associated kinase (JAK) inhibitor from L04AA45 filgotinib to L04AF04 filgotinib

15.3.21. Ganaxolone - ZTALMY (CAP) - EMEA/H/C/005825/II/0005, Orphan

Applicant: Marinus Pharmaceuticals Emerald Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.2 of the SmPC in order to update dosing instructions in severe hepatic impairment based on data from phase I study 1042-IHF-1001. The RMP version 1.3 has also been submitted

15.3.22. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/II/0019, Orphan

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Bianca Mulder

Scope: Update of section 5.1 of the SmPC in order to include the description of the final results from PAES study 17-HMedIdeS-14 listed as a specific obligation in the Annex II (SOB/002); this is a prospective, observational long-term follow-up study of patients treated with imlifidase (IdeS) prior to kidney transplantation. The primary objective of this trial was to evaluate graft survival in patients who have undergone kidney transplantation after imlifidase administration in earlier trials and relates to both safety and efficacy. The RMP version 1.2 has also been submitted. In addition, the MAH took the opportunity to update section E of Annex II and to implement editorial changes to sections 4.4, 4.6 and 9 of the SmPC. Furthermore, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.23. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0133/G

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

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

- 1) Update of section 4.2, 4.8 and 5.1 of the SmPC in order to add 3-IV induction dosing regimen and dose escalation of subcutaneous maintenance dose from CT-P13 SC 120 mg Q2W to 240 mg Q2W for patients with loss of response and update efficacy and safety information based on Week 54 data from studies CT-P13 3.7 (ulcerative colitis) and CT-P13 3.8 (Crohn's disease), listed as a category 3 study in the RMP; Study CT-P13 3.7 is a randomised, placebo controlled, double-blind, phase 3 study to evaluate the efficacy and safety of the subcutaneous injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active ulcerative colitis and study CT-P13 3.8 is a randomised, placebo-controlled, double-blind, phase 3 study to evaluate the efficacy and safety of the subcutaneous injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active Crohn's disease.
- 2) Update of section 4.2 and 5.2 of the SmPC in order to add subcutaneous induction posology and pharmacokinetic information based on Population PK and PK-PD Modelling and Simulation.
- 3) Update of section 4.2 of the SmPC in order to switch from high-dose IV maintenance (> 5 mg/kg) to subcutaneous maintenance dose of 120 mg every two weeks based on data from REMSWITCH study (Effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases: the REMSWITCH Study). The RMP version 16.1 has also been submitted. The package leaflet and labelling are

updated accordingly. In addition, the MAH took the opportunity to introduce minor updates to the product information

15.3.24. [Irinotecan hydrochloride trihydrate - ONIVYDE PEGYLATED LIPOSOMAL \(CAP\) - EMEA/H/C/004125/II/0034, Orphan](#)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: David Olsen

Scope: Extension of indication to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas for Onivyde in combination with oxaliplatin, 5 fluorouracil (5 FU) and leucovorin (LV) based on final results from phase 3 study NAPOLI 3 (D-US-60010-001): an interventional study with a primary objective to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. The updated RMP version 4.1 is also submitted

15.3.25. [Melatonin - SLENYTO \(CAP\) - EMEA/H/C/004425/II/0025](#)

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Extension of indication to include treatment of neurogenetic disorders (e.g., Angelman syndrome, Rett syndrome, Tuberous sclerosis complex and Williams syndrome) for SLENYTO, based on Phase III study NEU_CH_7911, post-marketing data and literature; As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.26. [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, multicenter, 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, multicentre, 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

15.3.27. Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/II/0019/G, Orphan

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Grouped application comprising two variations as follows:

Type II (C.I.4) – Update of sections 4.1 and 5.1 of the SmPC in order to rephrase the indication wording to align with the current WHO definitions. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet.

Type IB (C.I.11.z) - Submission of an updated RMP version 2.0 in order to align the safety concerns following the assessment of procedure EMEA/H/C/005167/11/0013

15.3.28. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0053/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Grouped application comprising two extensions of indication to include treatment of paediatric patients weighing at least 1.5 kg for VEKLURY, based on final results from study GS-US-540-5823; this is a Phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir in participants from birth to < 18 years of age with COVID-19; As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted

15.3.29. Ribociclib - KISQALI (CAP) - EMEA/H/C/004213/II/0045

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 CLEE011012301C (NATALEE); This is a global, Phase III, multicentre, 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

15.3.30. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0078

Applicant: BioMarin International Limited

PRAC Rapporteur: Eamon O'Murchu

Scope: Submission of the final report from study KOGNITO, listed as a category 3 study in the RMP. This is a phase IV open-label, single-cohort study of the long-term neurocognitive outcomes in 4- to 5-year-old children with phenylketonuria treated with sapropterin dihydrochloride (Kuvan) for 7 years. The RMP version 16.0 has also been submitted

15.3.31. Sarilumab - KEVZARA (CAP) - EMEA/H/C/004254/II/0044

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension of indication to include treatment of Polymyalgia Rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper for Kevzara, based on results from study EFC15160; this is a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica; 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 4.0 of the RMP is also submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection

15.3.32. Selpercatinib - RETSEVMO (CAP) - EMEA/H/C/005375/II/0028

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Bianca Mulder

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on interim results from study LIBRETTO-431 (JZJC) listed as a specific obligation in the Annex II (SOB/002); this is a randomised Phase 3 study comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive NSCLC. The package leaflet is updated accordingly. The RMP version 6.1 has also been submitted. In addition, the MAH took the opportunity to update Annex II

15.3.33. Setmelanotide - IMCIVREE (CAP) - EMEA/H/C/005089/II/0018, Orphan

Applicant: Rhythm Pharmaceuticals Netherlands B.V.

PRAC Rapporteur: Anna Mareková

Scope: Extension of indication to include the population of children aged 2 years and above for the treatment of pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin Type 1 (PCSK1) deficiency or biallelic leptin receptor (LEPR) deficiency and Bardet-Biedl Syndrome (BBS) for IMCIVREE, based on the final results from study RM-493-033 "A Phase 3 multicentre, one-year, open-label study of setmelanotide in paediatric patients aged 2 to <6 years of age with rare genetic causes of obesity"; this is an open label study to evaluate the weight-related parameters along with the safety and tolerability of setmelanotide in patients aged 2 to <6 years. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the product information

15.3.34. Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0100

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Update of section 5.1 of the SmPC in order to add vaccine effectiveness data, and the removal of the two open specific obligations (POX-MVA-039 (SOB02) and SEMVAc (SOB03)), based on the IMVANEX vaccine effectiveness data in real-world use during the 2022 monkeypox outbreak. Consequently, the MAH proposes a switch from exceptional marketing authorisation to full marketing authorisation. The Annex II and package leaflet are updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.35. Spesolimab - SPEVIGO (CAP) - EMEA/H/C/005874/X/0006/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nathalie Gault

Scope: Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (150 mg) and new route of administration (subcutaneous use), for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age. This line extension is grouped with a type II variation (C.I.6.a) to extend indication for Spevigo 450 mg concentrate for solution for infusion to include treatment of generalised pustular psoriasis (GPP) flares in adolescents (from 12 years of age), based on final results from study 1368-0027 (Effisayil 2) and extrapolation; this is a multi-centre, randomised, parallel group, double blind, placebo controlled, phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (spesolimab) compared to placebo in preventing GPP flares in patients with history of GPP. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Annex II and package leaflet 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 editorial changes to the product information and update the list of local representatives in the package leaflet

15.3.36. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/II/0054

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to update clinical and safety information based on long-term results from the extension periods of the pivotal clinical studies MK-3222-010 (A 64-Week, Phase 3, Randomised, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects with Moderate-to-Severe Chronic Plaque Psoriasis (Protocol No. MK-3222-010)) and MK-3222-011 (A 52-Week, Phase 3, Randomised, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222 / MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis). The RMP

version 1.4 has also been submitted

15.3.37. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0121

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of the final report from study ZUMA-8 (PAM). This is a phase 1 multicenter study evaluating the safety and tolerability of KTE-X19 in adult subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma. The RMP version 29.0 has also been submitted

15.3.38. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0201

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Update of sections 4.5, 4.8 and 5.1 of the SmPC in order to update information regarding concomitant vaccine administration with influenza vaccine based on final results from study C4591030 listed as a category 3 study in the RMP. This is an interventional phase 3, randomised, observer-blind trial to evaluate the safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly in adults 18 to 64 years of age. The package leaflet is updated accordingly. The RMP version 11.1 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. Ataluren - TRANSLARNA³⁶ (CAP) - PSUSA/00010274/202307

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

³⁶ [EMA confirms recommendation for non-renewal of authorisation of Duchenne muscular dystrophy medicine Translarna | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/en/press/news/2024/01/ema-confirms-recommendation-for-non-renewal-of-authorisation-of-duchenne-muscular-dystrophy-medicine-translarna)

16.1.2. Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202308

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Bimekizumab - BIMZELX (CAP) - PSUSA/00010953/202308

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.4. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202307

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Catridecacog - NOVOTHIRTEEN (CAP) - PSUSA/00010034/202307

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.6. Corifollitropin alfa - ELONVA (CAP) - PSUSA/00000875/202307

Applicant: Organon N.V.

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.7. Difelikefalin - KAPRUVIA (CAP) - PSUSA/00010995/202308

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.8. Eptinezumab - VYEPTI (CAP) - PSUSA/00010966/202308

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.9. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202308

Applicant: Ultragenyx Germany GmbH
PRAC Rapporteur: Mari Thorn
Scope: Evaluation of a PSUSA procedure

16.1.10. Evolocumab - REPATHA (CAP) - PSUSA/00010405/202307

Applicant: Amgen Europe B.V.
PRAC Rapporteur: Kimmo Jaakkola
Scope: Evaluation of a PSUSA procedure

16.1.11. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202308

Applicant: Holostem S.r.l., ATMP
PRAC Rapporteur: Eamon O'Murchu
Scope: Evaluation of a PSUSA procedure

16.1.12. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202308

Applicant: Bristol-Myers Squibb Pharma EEIG
PRAC Rapporteur: Sonja Hrabcik
Scope: Evaluation of a PSUSA procedure

16.1.13. Hydrocortisone³⁷ - ALKINDI (CAP) - PSUSA/00010674/202308

Applicant: Diurnal Europe BV
PRAC Rapporteur: Mari Thorn
Scope: Evaluation of a PSUSA procedure

16.1.14. Ibuprofen³⁸ - PEDEA (CAP) - PSUSA/00001712/202307

Applicant: Recordati Rare Diseases
PRAC Rapporteur: Rhea Fitzgerald
Scope: Evaluation of a PSUSA procedure

16.1.15. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202308

Applicant: Takeda Pharmaceuticals International AG Ireland Branch
PRAC Rapporteur: Kirsti Villikka

³⁷ Centrally authorised products indicated for treatment of adrenal insufficiency, paediatric use only

³⁸ Indicated in ductus arteriosus

Scope: Evaluation of a PSUSA procedure

16.1.16. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202308

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.17. Lenacapavir - SUNLENCA (CAP) - PSUSA/00011012/202308

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.18. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202308

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.19. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202307

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.20. Melphalan flufenamide - PEPAXTI (CAP) - PSUSA/00011013/202308

Applicant: Oncopeptides AB

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.21. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - PSUSA/00002017/202307

Applicant: Roche Registration GmbH

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.22. Mitapivat - PYRUKYND (CAP) - PSUSA/00011025/202308

Applicant: Agios Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.23. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202308

Applicant: Pharmaand GmbH

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.24. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202308

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.25. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202308

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.26. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202308

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.27. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/202307

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Karin Ernehalm

Scope: Evaluation of a PSUSA procedure

16.1.28. Saxagliptin – ONGLYZA (CAP); saxagliptin, metformin - KOMBOGLYZE (CAP) - PSUSA/00002685/202307

Applicant: AstraZeneca AB

PRAC Rapporteur: Bianca Mulder

Scope: Evaluation of a PSUSA procedure

16.1.29. Sotrovimab - XEVDY (CAP) - PSUSA/00010973/202308

Applicant: Glaxosmithkline Trading Services Limited

PRAC Rapporteur: Liana Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.30. Sutimlimab - ENJAYMO (CAP) - PSUSA/00011023/202308

Applicant: Sanofi B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.31. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202307

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Teclistamab - TECVAYLI (CAP) - PSUSA/00011010/202308

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jana Lukacisinova

Scope: Evaluation of a PSUSA procedure

16.1.33. Temozolomide - TEMODAL (CAP) - PSUSA/00002886/202307

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.34. Tisagenlecleucel - KYMRIA H (CAP) - PSUSA/00010702/202308

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.35. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202307

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

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. Aripiprazole - ABILIFY (CAP); ABILIFY MAINTENA (CAP); ARIPIPRAZOLE SANDOZ (CAP); NAP - PSUSA/00000234/202307

Applicant: Otsuka Pharmaceutical Netherlands B.V. (Abilify, Abilify Maintena), Sandoz GmbH (Aripiprazole Sandoz), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.2.2. Eflornithine³⁹ - VANIQA (CAP); NAP - PSUSA/00001202/202307

Applicant: Almirall S.A (Vaniqa), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Aciclovir, hydrocortisone (NAP) - PSUSA/00009004/202307

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Colchicine (NAP) - PSUSA/00000858/202307

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.3. Donepezil, memantine (NAP) - PSUSA/00011039/202307

Applicant(s): various

PRAC Lead: Jana Lukačšínová

Scope: Evaluation of a PSUSA procedure

16.3.4. Ezetimibe, rosuvastatin (NAP) - PSUSA/00010271/202307

Applicant(s): various

PRAC Lead: Barbara Kovačić Bytyqi

³⁹ Topical use only

Scope: Evaluation of a PSUSA procedure

16.3.5. Fenofibrate (NAP) - PSUSA/00001362/202307

Applicant(s): various

PRAC Lead: Jo Robays

Scope: Evaluation of a PSUSA procedure

16.3.6. Indometacin (NAP) - PSUSA/00001738/202307

Applicant(s): various

PRAC Lead: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.3.7. Inosine pranobex (NAP) - PSUSA/00010425/202308

Applicant(s): various

PRAC Lead: Irina Sandu

Scope: Evaluation of a PSUSA procedure

16.3.8. Niclosamide (NAP) - PSUSA/00002151/202308

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.3.9. Ribavirin⁴⁰ (NAP)⁴¹ - PSUSA/00010007/202307

Applicant(s): various

PRAC Lead: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/II/0254

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Monica Martinez Redondo

⁴⁰ Oral formulation(s) only

⁴¹ Ribavirin - REBETOL (CAP) - European Commission (EC) decision on the withdrawal of the marketing authorisation (MA) dated 18 October 2023

Scope: Update of section 4.8 of the SmPC in order to update the frequency of Adverse Drug Reaction (ADR) 'glomerulonephritis' from 'not known' to 'rare' following PSUSA/00010795/202302 procedure, based on available evidence from clinical trials, literature, and post-marketing data. The package leaflet is updated accordingly

16.6. Expedited summary safety reviews⁴²

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)⁴³

17.1.1. Blinatumomab - Blincyto (CAP) - EMEA/H/C/PSA/S/0111

Applicant: Sanofi Belgium

PRAC Rapporteur: Jana Lukacisinova

Scope: Substantial amendment to a protocol for an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁴

17.2.1. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/MEA 002.7

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: MAH's response to MEA 002.6 [Revised Protocol / Study Number: AVA-CLD-402] as per RSI as adopted in October 2023

17.2.2. Cabotegravir - APRETUDE (CAP) - EMEA/H/C/005756/MEA 003

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Protocol for study CAB LA PrEP Cohort: Prospective Cohort Study to Assess Adherence and Effectiveness of, and Monitor for Hepatotoxicity and Resistance to Cabotegravir for Pre-Exposure Prophylaxis in Europe

⁴² 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

⁴³ In accordance with Article 107n of Directive 2001/83/EC

⁴⁴ 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. Cannabidiol - EPIDYOLEX (CAP) - EMEA/H/C/004675/MEA 007.4

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Revised Protocol v. for study GWEP19022 (listed as a category 3 study in the RMP): a prospective, observational cohort long-term safety study to assess the potential for chronic liver injury in patients treated with Epidyolex (cannabidiol oral solution) when used under conditions of routine clinical care as per the request for supplementary information (RSI) adopted in November 2023

17.2.4. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.5

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Amended PASS protocol / Study number: 20190404; Title: Use of Erythropoiesis Stimulating Agents (ESAs) in Subjects Receiving Myelosuppressive Chemotherapy in Europe

17.2.5. Eptinezumab - VYEPTI (CAP) - EMEA/H/C/005287/MEA 004.4

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to MEA 004.3 [Revised Protocol - Master Study No. 19756N; Observational, historical cohort study of patients initiating eptinezumab in routine clinical practice and is investigating the long-term cardiovascular safety and real-world use of Eptinezumab] as per the request for supplementary information (RSI) adopted in October 2023

17.2.6. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 001.9

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol amendment for study TEG4001: a prospective, non-interventional, long-term, multinational cohort safety study of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

17.2.7. Mogamulizumab - POTELIGEO (CAP) - EMEA/H/C/004232/MEA 001.4

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: From Initial MAA: REVISED PROTOCOL 0.3 FOR PASS EUPAS31436 To Characterise the Safety of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab

17.2.8. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.5

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Early study termination proposal with the original justification document - Clinical Study Protocol PASS 3000-04-001 Version 8

Draft protocol amendment for EUPAS 29407 (in track changes) incorporating the changes related to the early termination proposal:

- New proposed end of data collection (data cut-off date): Q2 2024 (current date: Q3 2026)
- New proposed final report submission: Q4 2024 (current date: Q1 2027)
- Removal of the exploratory objective and related information

17.2.9. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004835/MEA 001.3

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the Ozanimod Real World Safety:

A Post Authorisation Multi National Long term Non Interventional Study (ORION) study (Categ. 3) protocol for approval within 6 months after the marketing authorisation for Zeposia is granted.

***Revised protocol / IM047-009 (ORION) version 5.0 ***

[future due date(s):

Interim study results: 31 Dec. 2025

Final CSR: 31 Dec. 2031]

17.2.10. Voclosporin - LUPKYNIS (CAP) - EMEA/H/C/005256/MEA 002.2

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 002.1 [PASS Protocol No 348-201-00021] as adopted in November 2023. Observational PASS in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin (category 3 study in the RMP)

17.3. Results of PASS imposed in the marketing authorisation(s)⁴⁵

17.3.1. Acridinium - BRETARIS GENUAIR (CAP); EKLIRA GENUAIR (CAP); acridinium, formoterol fumarate dihydrate – BRIMICA GENUAIR (CAP), DUAKLIR GENUAIR (CAP) - EMEA/H/C/PSR/S/0047

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Final study report for a PASS to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for acridinium bromide as monotherapy and fixed-dose combination of acridinium/formoterol

⁴⁵ In accordance with Article 107p-q of Directive 2001/83/EC

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁶

17.4.1. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/II/0033/G

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final reports from the Drug Utilisation Study of Intuniv (guanfacine extended release) in European countries: a prescriber survey (EUPAS18739) and a retrospective database study (EUPAS18735), listed as category 3 studies in the RMP. The RMP version 4.0 has also been submitted

17.4.2. Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0096

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update long-term safety information based on final results from studies 161406 "Non-Interventional Post-Marketing Safety Study on the Long-Term Safety of HYQVIA (Global)" listed as category 3 a study in the RMP and 161302 "Non-Interventional PASS on the Long-Term Safety of HyQvia in Subjects Treated with HyQvia". Both studies were non-interventional, prospective, uncontrolled, multicenter, open-label, post-authorisation studies. The RMP version 15.0 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, to update the list of local representatives in the package leaflet and to introduce minor editorial changes to the product information

17.4.3. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0081

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on final results from study Vedolizumab-5001 (OTIS Entyvio Pregnancy Exposure Registry); this is a non-interventional study to monitor planned and unplanned pregnancies in female patients with ulcerative colitis or Crohn's disease. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes and corrections to the product information and bring it in line with the latest QRD template

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

17.5.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 021.1

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

⁴⁶ 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

Scope: From II-0068 and II-0075 (RMP); Second Annual Safety Report; Intraocular Pressure Increase with the Eylea PFS

17.5.2. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.16

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: From initial MAA; Ninth Annual Progress Report, Study (PASS) OBS13434 (non-imposed/non-interventional); This annual progress report covers the period from 01-Jan-2023 to 06-Oct-2023. A progress report will be compiled on an annual basis in order to meet applicable regulatory commitments. Study data for patient demographics and baseline disposition as well as an overview of all adverse events including AESIs and serious adverse events is no longer included in the annual PASS progress report as agreed with the procedure manager at time of previous PASS annual progress report 3

17.5.3. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.5

Applicant: Sanofi Belgium

PRAC Rapporteur: Karin Erneholm

Scope: PASS Mortality Interim Study Result / CSA0002; REAL WORLD AND EPIDEMIOLOGY STUDY REPORT; A non-interventional PASS to investigate the risk of mortality in multiple sclerosis patients treated with alemtuzumab (LEMTRADA) relative to comparable multiple sclerosis patients using other disease modifying therapies: A cohort study

17.5.4. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/SOB 009.2

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Bianca Mulder

Scope: MAH's responses to SOB009.1 [Study BLU-285-1406 is a multinational, open-label, observational PASS that will evaluate the long-term safety and efficacy of avapritinib for the first-line treatment or following ≤ 4 months of imatinib treatment in at least 50 patients with PDGFRA D842V-mutated GIST.] RSI as adopted in November 2023

17.5.5. Benralizumab - FASENRA (CAP) - EMEA/H/C/004433/MEA 004.7

Applicant: AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Third interim report for study D3250R00042: a descriptive study of the incidence of malignancy in patients with severe asthma overall and among those receiving benralizumab and other therapies in real-world settings

17.5.6. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 005.1

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Martirosyan

Scope: MAH's response to questions on MEA 005 [Study PS0014] as adopted in November 2023

17.5.7. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 004.5

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 004.4 [Protocol, study no. 2019nCoV-402] as per RSI as adopted in October 2023

17.5.8. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 009.4

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: 4th interim report of study MB102118: Pharmacoepidemiology study assessing the risk of cancer. Evaluate cancer (Study MB102-118ST/D1690R00007 - (EUPAS12116))

17.5.9. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 004.9

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: 4th interim report of study MB102118: Pharmacoepidemiology study assessing the risk of cancer. Evaluate cancer (Study MB102-118ST/D1690R00007 -(EUPAS12116))

17.5.10. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.15

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Tenth Annual Interim Safety Report for Study C1CL670E2422; An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload

17.5.11. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.2

Applicant: Alexion Europe SAS

PRAC Rapporteur: Monica Martinez Redondo

Scope: aHUS Registry Biennial Interim Report /Protocol M11-001; Title: An Observational, non-interventional multicenter, multinational study of patients with atypical hemolytic-uremic syndrome

17.5.12. Esketamine - SPRAVATO (CAP) - EMEA/H/C/004535/MEA 003.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Interim Study /Study no.: PCSNSP002812; Survey to Assess the Effectiveness of SPRAVATO Educational Materials for Additional Risk Minimization Measures in the European Union

17.5.13. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: FOURTH interim report of the open-label extension phase of study CFTY720D2311 to collect long term safety data (RMP Category 3 study). Study CFTY720D2311: A two-year, double-blind, randomised, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β -1a i.m. once weekly in pediatric patients with multiple sclerosis with five-year fingolimod Extension Phase

17.5.14. Galcanezumab - EMGALITY (CAP) - EMEA/H/C/004648/MEA 003.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: From Initial MAA: Galcanezumab European Drug Utilization and Safety Outcomes Study (Planned).

- To describe, in real-world clinical practice, the utilization of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardio-vascular events, and malignancies.

- The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, as feasible, to conduct comparative safety analyses of serious cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control. (Cat. 3)

17.5.15. Human C1-esterase inhibitor - CINRYZE (CAP) - EMEA/H/C/001207/MEA 021.1

Applicant: Takeda Manufacturing Austria AG

PRAC Rapporteur: Gabriele Maurer

Scope: IOS interim Clinical Study Report; Encompassing data of 199 Cinryze-treated patients. Additionally, at least 45 unique SHP616-401

17.5.16. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.6

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Third Annual Interim Study Report / VX20-445-120; Title: Real-World Effects and Utilisation Patterns of Elexacaftor, Tezacaftor, and Ivacaftor Combination Therapy (ELX/TEZ/IVA) in Patients with Cystic Fibrosis (CF)

17.5.17. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/MEA 001.7

Applicant: Shionogi B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: 2nd Annual Progress Report with interim report of study results for An Observational PASS of Patients with Chronic Opioid Use for Non-Cancer and Cancer Pain who have Opioid-Induced Constipation (OIC)

17.5.18. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/ANX 001

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Gabriele Maurer

Scope: From initial MAA: Fifth Progress Report (yearly) and Second Interim Report for PASS NN7999-4031/Paradigm 8: A Non-Interventional PASS in male haemophilia B patients receiving Nonacog Beta Pegol

17.5.19. Ofatumumab - KESIMPTA (CAP) - EMEA/H/C/005410/MEA 002.4

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: SECOND INTERIM REPORT for PASS Study COMB157G2407 (cat. 3): Evaluation of pregnancy and infant outcomes in Kesimpta patients using PRenancy outcomes Intensive Monitoring (PRIM) data – The Kesimpta-PRIM study

17.5.20. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.6

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: SECOND INTERIM REPORT for Study 165-501; A prospective, global observational exposure study. Title: A Multi-Center, Observational Study to Evaluate the Long Term Safety of Subcutaneous Injections of Pegvaliase in Patients with Phenylketonuria

17.5.21. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.8

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Second Interim Report / study number: 165-504; Title: A global multicentre study to assess maternal, fetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.5.22. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁴⁷) - EMEA/H/W/002300/MEA 003.9

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Ninth Progress Report for Study EPI-MAL-003: Estimate the incidence of protocol-defined potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with RTS,S/AS01E enrolled during the EPI-MAL-003 study

17.5.23. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/ANX 001.6

Applicant: Alexion Europe SAS

PRAC Rapporteur: Mari Thorn

Scope: From Initial MAA: Non-interventional PASS: LAL Deficiency Registry: Non-interventional, multicentre, prospective disease and clinical outcome registry of patients with Lysosomal Acid Lipase Deficiency to further understand the disease, its progression and any associated complication, and to evaluate the long-term efficacy (normalisation of hepatic function) and safety of Kanuma (in particular hypersensitivity reactions, including anaphylaxis, and anti-drug antibodies development potentially impacting response to drug) according to agreed protocol

17.5.24. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.8

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: FOURTH Annual Interim Results/ Study No.: M-14745-40; Title: Tildrakizumab PASS in European Psoriasis Registries

17.5.25. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 041.5

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Liana Martirosyan

Scope: Third Interim Report / Study C4591036; Clinical study to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis

17.5.26. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/MEA 029

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Annual Report for the Gaucher Outcome Survey (GOS) 2023; Title: Gaucher Disease Outcome Survey (GOS) An Observational, International, Multi-center, Long-term Registry of

⁴⁷ 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)

Patients with Gaucher Disease

17.5.27. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/MEA 005.4

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: First Biannual Report / BMN111-603 (period from 17 Apr 2023 to 25 Aug 2023); A multicenter, non-interventional study to evaluate long-term safety in patients with achondroplasia treated with Voxzogo (vosoritide)

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. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/S/0064 (without RMP)

Applicant: Gentium S.r.l.

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0020 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Bianca Mulder

Scope: Conditional renewal of the marketing authorisation

18.2.2. Futibatinib - LYTGObI (CAP) - EMEA/H/C/005627/R/0003 (without RMP)

Applicant: Taiho Pharma Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.3. Glofitamab - COLUMVI (CAP) - EMEA/H/C/005751/R/0003 (with RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jana Lukacisinova

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Angiotensin II - GIAPREZA (CAP) - EMEA/H/C/004930/R/0027 (without RMP)

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Bianca Mulder

Scope: 5-year renewal of the marketing authorisation

18.3.2. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/R/0037 (without RMP)

Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.3. Deferasirox - DEFERASIROX MYLAN (CAP) - EMEA/H/C/005014/R/0013 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.4. Trientine - CUFENCE (CAP) - EMEA/H/C/004111/R/0016 (without RMP)

Applicant: Univar Solutions BV

19. Annex II – List of participants

including any restrictions with respect to involvement of members/alternates/experts following evaluation of declared interests for the 4 March 2024 PRAC meeting, which was held remotely.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	
Jan Neuhauser	Member	Austria	No interests declared	
Sonja Hrabcik	Alternate	Austria	No interests declared	
Jean-Michel Dogné	Member	Belgium	No interests declared	
Jo Robays	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	
Petar Mas	Member	Croatia	No interests declared	
Barbara Bytyqi	Member	Croatia	No interests declared	
Elena Kaisis	Member	Cyprus	No interests declared	
Panagiotis Psaras	Alternate	Cyprus	No interests declared	
Eva Jirsová	Member	Czechia	No interests declared	
Jana Lukacisinova	Alternate	Czechia	No interests declared	
Marie Louise Schougaard Christiansen	Member	Denmark	No interests declared	
Karin Erneholm	Alternate	Denmark	No interests declared	
Maia Uusküla	Member	Estonia	No interests declared	
Kirsti Villikka	Member	Finland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kimmo Jaakkola	Alternate	Finland	No interests declared	
Tiphaine Vaillant	Member	France	No interests declared	
Nathalie Gault	Alternate	France	No interests declared	
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer	Alternate	Germany	No restrictions applicable to this meeting	
Sofia Trantza	Member	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	<p>16.1.12. Fedratinib - INREBIC (CAP) - PSUSA/000109 09/202308</p> <p>16.1.18. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/000109 90/202308</p> <p>17.2.9. Ozanimod - ZEPOSIA (CAP) - EMEA/H/C/004 835/MEA 001.3</p>
Guðrún Stefánsdóttir	Member	Iceland	No participation in final deliberations and voting on:	<p>15.2.2. Romiplostim - NPLATE (CAP) - EMEA/H/C/000 942/II/0091</p> <p>15.3.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004 212/X/0036/G</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				15.3.5. Apremilast - OTEZLA (CAP) - EMEA/H/C/003 746/II/0044/G 16.1.10. Evolocumab - REPATHA (CAP) - PSUSA/000104 05/202307 17.2.4. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000 332/MEA 092.5
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	
Amelia Cupelli	Member	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Rugile Pilviniene	Member	Lithuania	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	
John Joseph Borg	Member	Malta	No interests declared	
Liana Martirosyan	Member	Netherlands	No interests declared	
Bianca Mulder	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation	6.1.4. Darolutamide - NUBEQA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in final deliberations and voting on:	- PSUSA/00010843/202307 17.5.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 021.1
Pernille Harg	Alternate	Norway	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Carla Torre	Alternate	Portugal	No interests declared	
Roxana Dondera	Member	Romania	No interests declared	
Irina Sandu	Alternate	Romania	No interests declared	
Miroslava Gocova	Alternate	Slovakia	No interests declared	
Polona Golmajer	Member	Slovenia	No interests declared	
Marjetka Plementas	Alternate	Slovenia	No interests declared	
Maria del Pilar Rayon	Member	Spain	No interests declared	
Monica Martinez Redondo	Alternate	Spain	No interests declared	
Ulla Wändel Liminga	Member	Sweden	No interests declared	
Mari Thorn	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano	Member	Independent scientific expert	No interests declared	
Milou-Daniel Drici	Member	Independent scientific expert	No interests declared	
Teresa Herdeiro	Member	Independent scientific expert	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No restrictions applicable to this meeting	
Hedvig Marie Egeland Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Antonio Giuseppe Messina	Alternate	Healthcare Professionals' Representative	No interests declared	
Michal Rataj	Alternate	Patients' Organisation Representative	No interests declared	
Laurence de Fays	Expert	Belgium	No interests declared	
Fabrice Moore	Expert	Belgium	No interests declared	
Françoise Wuillaume	Expert	Belgium	No interests declared	
Ivana Ljubičić	Expert	Croatia	No interests declared	
Veronika Descikova	Expert	Czechia	No interests declared	
Anna Kroupova	Expert	Czechia	No interests declared	
Lucie Skálová	Expert	Czechia	No interests declared	
Marian Hjortlund Allon	Expert	Denmark	No interests declared	
Hanna Belcik Christensen	Expert	Denmark	No restrictions applicable to this meeting	
Alexander Braathen	Expert	Denmark	No interests declared	
Nicklas Hasselblad Lundstrøm	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
Charlotte Hejl	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul	Expert	Denmark	No interests declared	
Kristina Laursen	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	
Aynur Sert	Expert	Denmark	No interests declared	
Per Sindahl	Expert	Denmark	No interests declared	
Helene Stenbæk Hansen	Expert	Denmark	No restrictions applicable to this meeting	
Violaine Closson-Carella	Expert	France	No interests declared	
Samuel Crommelynck	Expert	France	No interests declared	
Nathalie Dumarcet	Expert	France	No interests declared	
Dina Habib-Hanawy	Expert	France	No interests declared	
Stephanie Hueber	Expert	France	No interests declared	
Jean-Michel Race	Expert	France	No interests declared	
Dennis Lex	Expert	Germany	No interests declared	
Joseph De Courcey	Expert	Ireland	No interests declared	
Finbarr Leacy	Expert	Ireland	No interests declared	
Maura O'Donovan	Expert	Ireland	No interests declared	
Darren Scully	Expert	Ireland	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Diāna Litenboka	Expert	Latvia	No interests declared	
Margje Monster-Simons	Expert	Netherlands	No interests declared	
Paul ten Berg	Expert	Netherlands	No interests declared	
Lies van Vlijmen	Expert	Netherlands	No interests declared	
Maria Vanenburg	Expert	Netherlands	No interests declared	
Sophia Venzke	Expert	Netherlands	No interests declared	
Frederika Adriana Vermeij-van Nimwegen	Expert	Netherlands	No restrictions applicable to this meeting	
Anita Volkers	Expert	Netherlands	No interests declared	
Inge Zomerdijk	Expert	Netherlands	No interests declared	
João Fernandes	Expert	Portugal	No interests declared	
Gal Christian Žvegelj	Expert	Slovenia	No interests declared	
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Charlotte Backman	Expert	Sweden	No interests declared	
Sissela Liljeqvist	Expert	Sweden	No restrictions applicable to this meeting	

A representative from the European Commission attended the meeting

Observers from Health Canada (Canada), FDA (USA), PMDA (Japan) and WHO 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: [Referral procedures: human medicines | European Medicines Agency \(europa.eu\)](#)

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>