



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2023
EMA/PRAC/452701/2023
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 28-31 August 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the [PRAC meeting highlights](#) once the procedures are finalised.

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

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents ([EMA/127362/2006, Rev. 1](#)).

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



Table of contents

1.	Introduction	14
1.1.	Welcome and declarations of interest of members, alternates and experts	14
1.2.	Agenda of the meeting on 28-31 August 2023	14
1.3.	Minutes of the previous meeting on 03-06 July 2023	14
2.	EU referral procedures for safety reasons: urgent EU procedures	14
2.1.	Newly triggered procedures	14
2.2.	Ongoing procedures	14
2.3.	Procedures for finalisation.....	14
3.	EU referral procedures for safety reasons: other EU referral procedures	15
3.1.	Newly triggered procedures	15
3.2.	Ongoing procedures	15
3.2.1.	Pseudoephedrine (NAP); pseudoephedrine, acetylsalicylic acid (NAP); pseudoephedrine, acetylcysteine, paracetamol (NAP); pseudoephedrine, acrivastine (NAP); pseudoephedrine, ascorbic acid, paracetamol (NAP); pseudoephedrine, cetirizine (NAP); pseudoephedrine, ebastine (NAP); pseudoephedrine, guaifenesin (NAP); pseudoephedrine, ibuprofen (NAP); pseudoephedrine, chlorphenamine (NAP); pseudoephedrine, chlorphenamine, codeine (NAP); pseudoephedrine, chlorphenamine, dextromethorphan (NAP); pseudoephedrine, chlorphenamine, paracetamol (NAP); pseudoephedrine, chlorphenamine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan (NAP); pseudoephedrine, dextromethorphan, paracetamol (NAP); pseudoephedrine, dextromethorphan, ascorbic acid, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, paracetamol (NAP); pseudoephedrine, dextromethorphan, guaifenesin, triprolidine (NAP); pseudoephedrine, dextromethorphan, triprolidine (NAP); pseudoephedrine, diphenhydramine, paracetamol (NAP); pseudoephedrine, doxylamine, paracetamol (NAP); pseudoephedrine, loratadine (NAP); pseudoephedrine, paracetamol (NAP); pseudoephedrine, paracetamol, pholcodine (NAP); pseudoephedrine, triprolidine (NAP); pseudoephedrine, triprolidine, guaifenesin (NAP); pseudoephedrine, triprolidine, paracetamol (NAP); pseudoephedrine, desloratadine - AERINAZE (CAP) – EMA/H/A-31/1526	15
3.3.	Procedures for finalisation.....	16
3.3.1.	Topiramate (NAP); topiramate, phentermine (NAP) - EMEA/H/A-31/1520	16
3.4.	Re-examination procedures.....	18
3.5.	Others	18
4.	Signals assessment and prioritisation	18
4.1.	New signals detected from EU spontaneous reporting systems	18
4.1.1.	Nivolumab – OPDIVO (CAP), OPDUALAG (CAP).....	18
4.2.	New signals detected from other sources	19
4.2.1.	Ipilimumab – YERVOY (CAP)	19
4.3.	Signals follow-up and prioritisation.....	20
4.3.1.	Acetazolamide (NAP).....	20

4.3.2.	Megestrol (NAP)	20
4.4.	Variation procedure(s) resulting from signal evaluation	21
5.	Risk management plans (RMPs)	21
5.1.	Medicines in the pre-authorisation phase	21
5.1.1.	Arpraziquantel - EMEA/H/W/004252	21
5.1.2.	Elranatamab - EMEA/H/C/005908, PRIME, Orphan.....	21
5.1.3.	Exagamglogene autotemcel - EMEA/H/C/005763, PRIME, Orphan.....	21
5.1.4.	Fidanacogene elaparvovec - EMEA/H/C/004774, PRIME, Orphan.....	21
5.1.5.	Germanium (⁶⁸ Ge) chloride, gallium (⁶⁸ Ga) chloride - EMEA/H/C/006053.....	22
5.1.6.	Leriglitazone - EMEA/H/C/005757, Orphan.....	22
5.1.7.	Momelotinib - EMEA/H/C/005768, Orphan	22
5.1.8.	Rozanolixizumab - EMEA/H/C/005824, Orphan.....	22
5.1.9.	Tofersen - EMEA/H/C/005493, Orphan	22
5.1.10.	Ustekinumab - EMEA/H/C/006101	22
5.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	22
5.2.1.	Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/II/0006	22
5.3.	Medicines in the post-authorisation phase – CHMP-led procedures	23
5.3.1.	Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0133	23
6.	Periodic safety update reports (PSURs)	24
6.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	24
6.1.1.	(1r,2s,5s)-n-{(1s)-1-cyano-2-[(3s)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-n-(trifluoroacetyl)-l-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide / ritonavir (Paxlovid) - PAXLOVID (CAP) - PSUSA/00010984/202212.....	24
6.1.2.	Abatacept - ORENCIA (CAP) - PSUSA/00000013/202212.....	25
6.1.3.	Brexucabtagene autoleucel - TECARTUS (CAP) - PSUSA/00010903/202301	25
6.1.4.	Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202301	26
6.1.5.	Dolutegravir - TIVICAY (CAP); dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP); dolutegravir, lamivudine - DOVATO (CAP) - PSUSA/00010075/202301.....	27
6.1.6.	Ibritumomab tiuxetan - ZEVALIN (CAP) - PSUSA/00001704/202302	28
6.1.7.	Relugolix - ORGOVYX (CAP) - PSUSA/00010994/202301	28
6.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	29
6.2.1.	Abacavir - ZIAGEN (CAP); NAP - PSUSA/00000010/202212	29
6.2.2.	Abacavir, lamivudine - KIVEXA (CAP); NAP - PSUSA/00000011/202212	29
6.2.3.	Abacavir, lamivudine, zidovudine - TRIZIVIR (CAP); NAP - PSUSA/00003144/202212	30
6.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	31
6.3.1.	Acebutolol (NAP) - PSUSA/00000018/202212	31
6.3.2.	Gemcitabine (NAP) - PSUSA/00001519/202301.....	31

6.3.3.	Paroxetine (NAP) - PSUSA/00002319/202212	32
6.4.	Follow-up to PSUR/PSUSA procedures	33
6.5.	Variation procedure(s) resulting from PSUSA evaluation	33
6.6.	Expedited summary safety reviews	33
7.	Post-authorisation safety studies (PASS)	33
7.1.	Protocols of PASS imposed in the marketing authorisation(s).....	33
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	33
7.2.1.	Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 012	33
7.3.	Results of PASS imposed in the marketing authorisation(s).....	34
7.3.1.	Roflumilast – DAXAS (CAP) - EMEA/H/C/PSR/S/0041	34
7.3.2.	Valproate (NAP) - EMEA/H/N/PSR/J/0036	35
7.4.	Results of PASS non-imposed in the marketing authorisation(s).....	36
7.4.1.	Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0082	36
7.4.2.	Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0100.....	37
7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	38
7.5.1.	Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/MEA 003.2	38
7.6.	Others	38
7.7.	New Scientific Advice	38
7.8.	Ongoing Scientific Advice	39
7.9.	Final Scientific Advice (Reports and Scientific Advice letters)	39
8.	Renewals of the marketing authorisation, conditional renewal and annual reassessments	39
8.1.	Annual reassessments of the marketing authorisation	39
8.2.	Conditional renewals of the marketing authorisation	39
8.3.	Renewals of the marketing authorisation	39
9.	Product related pharmacovigilance inspections	39
9.1.	List of planned pharmacovigilance inspections.....	39
9.2.	Ongoing or concluded pharmacovigilance inspections.....	39
9.3.	Others	39
10.	Other safety issues for discussion requested by CHMP or EMA	39
10.1.	Safety related variations of the marketing authorisation.....	39
10.2.	Timing and message content in relation to Member States’ safety announcements	40
10.3.	Other requests.....	40
10.4.	Scientific Advice	40

11.	Other safety issues for discussion requested by the Member States	40
11.1.	Safety related variations of the marketing authorisation.....	40
11.2.	Other requests.....	40
12.	Organisational, regulatory and methodological matters	40
12.1.	Mandate and organisation of PRAC.....	40
12.1.1.	PRAC membership	40
12.1.2.	Vote by proxy	40
12.1.3.	PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2023	40
12.2.	Coordination with EMA Scientific Committees or CMDh-v	40
12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	41
12.4.	Cooperation within the EU regulatory network	41
12.4.1.	Health threats and EMA Emergency Task Force (ETF) activities - update.....	41
12.5.	Cooperation with International Regulators.....	41
12.6.	Contacts of PRAC with external parties and interaction with the Interested Parties to the Committee.....	41
12.7.	PRAC work plan	41
12.7.1.	PRAC work plan 2023 – update	41
12.8.	Planning and reporting	41
12.8.1.	EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q2 2023 and predictions.....	41
12.8.2.	PRAC workload statistics – Q2 2023	41
12.9.	Pharmacovigilance audits and inspections	42
12.9.1.	Pharmacovigilance systems and their quality systems	42
12.9.2.	Pharmacovigilance inspections	42
12.9.3.	Pharmacovigilance audits.....	42
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list	42
12.10.1.	Periodic safety update reports	42
12.10.2.	Granularity and Periodicity Advisory Group (GPAG)	42
12.10.3.	PSURs repository	42
12.10.4.	Union reference date list – consultation on the draft list	42
12.11.	Signal management.....	42
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group.....	42
12.12.	Adverse drug reactions reporting and additional monitoring.....	43
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	43
12.12.2.	Additional monitoring	43
12.12.3.	List of products under additional monitoring – consultation on the draft list	43

12.13.	EudraVigilance database.....	43
12.13.1.	Activities related to the confirmation of full functionality	43
12.14.	Risk management plans and effectiveness of risk minimisations.....	43
12.14.1.	Risk management systems	43
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations	43
12.14.3.	Risk management plan (RMP) of medicinal product(s) – update on the process of publication on EMA website	43
12.15.	Post-authorisation safety studies (PASS)	43
12.15.1.	Post-authorisation Safety Studies – imposed PASS	43
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS	44
12.16.	Community procedures.....	44
12.16.1.	Referral procedures for safety reasons	44
12.17.	Renewals, conditional renewals, annual reassessments.....	44
12.18.	Risk communication and transparency	44
12.18.1.	Public participation in pharmacovigilance	44
12.18.2.	Safety communication	44
12.19.	Continuous pharmacovigilance	44
12.19.1.	Incident management	44
12.20.	Impact of pharmacovigilance activities	44
12.20.1.	Revised process for prioritisation and regulatory follow-up of impact research (Rev.2)	44
12.21.	Others	44
12.21.1.	Guideline on clinical investigation of recombinant and human plasma-derived factor IX products and core SmPC – revision	44
12.21.2.	Patient Experience Data (PED) – priority activities and actions	45
13.	Any other business	45
14.	Annex I – Signals assessment and prioritisation	45
14.1.	New signals detected from EU spontaneous reporting systems.....	45
14.1.1.	Amphotericin B (NAP)	45
14.1.2.	Avatrombopag – DOPTLET (CAP)	45
14.1.3.	Cefotaxime (NAP)	45
14.1.4.	Cobimetinib – COTELLIC (CAP); Vemurafenib – ZELBORAF (CAP)	46
14.1.5.	Minoxidil (NAP).....	46
14.1.6.	Osimertinib – TAGRISSO (CAP)	46
14.1.7.	Palbociclib – IBRANCE (CAP)	46
14.2.	New signals detected from other sources.....	46
15.	Annex I – Risk management plans	47
15.1.	Medicines in the pre-authorisation phase.....	47
15.1.1.	Azacididine - EMEA/H/C/006154.....	47

15.1.2.	Eribulin - EMEA/H/C/006134	47
15.1.3.	Ibuprofen - EMEA/H/C/006129	47
15.1.4.	Paclitaxel - EMEA/H/C/006173	47
15.1.5.	Ranibizumab - EMEA/H/C/006055.....	47
15.1.6.	Zoonotic influenza vaccine (h5n1) (surface antigen, inactivated, adjuvanted) - EMEA/H/C/006375.....	47
15.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	47
15.2.1.	Acidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS2548/0051; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS2548/0052	47
15.2.2.	Acidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS2546/0039; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS2546/0040.....	48
15.2.3.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0043.....	48
15.2.4.	Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004137/WS2486/0025	48
15.2.5.	Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/WS2537/0021; Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/WS2537/0020; Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/WS2537/0024.....	48
15.2.6.	Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0017, Orphan.....	48
15.2.7.	Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2535/0053; NEPARVIS (CAP) - EMEA/H/C/004343/WS2535/0051	49
15.2.8.	Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/WS2541/0040; RYBELSUS (CAP) - EMEA/H/C/004953/WS2541/0035.....	49
15.2.9.	Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0064.....	49
15.2.10.	Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0013.....	49
15.2.11.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0054.....	49
15.3.	Medicines in the post-authorisation phase – CHMP-led procedures	50
15.3.1.	Abrocitinib - CIBINQO (CAP) - EMEA/H/C/005452/II/0010	50
15.3.2.	Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0069, Orphan.....	50
15.3.3.	Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0078.....	50
15.3.4.	Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0023, Orphan	51
15.3.5.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0037.....	51
15.3.6.	Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0107, Orphan.....	51
15.3.7.	Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/II/0021, Orphan	51
15.3.8.	Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/II/0027	52
15.3.9.	Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/X/0017/G.....	52
15.3.10.	Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/II/0011.....	53
15.3.11.	Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58) - EMEA/H/W/002320/II/0016.....	53
15.3.12.	Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0013/G, Orphan	54
15.3.13.	Human fibrinogen, human thrombin - VERASEAL (CAP) - EMEA/H/C/004446/II/0027.....	54
15.3.14.	Human normal immunoglobulin - HYQVIA (CAP) - EMEA/H/C/002491/II/0087	54

15.3.15.	Inotuzumab ozogamicin - BESPONSA (CAP) - EMEA/H/C/004119/II/0026, Orphan	54
15.3.16.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0035, Orphan .	55
15.3.17.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/II/0039, Orphan .	55
15.3.18.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/X/0033, Orphan .	55
15.3.19.	Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0045, Orphan	56
15.3.20.	Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/X/0034/G, Orphan	56
15.3.21.	Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0050	56
15.3.22.	Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0080.....	56
15.3.23.	Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0027.....	57
15.3.24.	Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/X/0132.....	57
15.3.25.	Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0064	57
15.3.26.	Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/II/0040, Orphan .	58
15.3.27.	Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0052.....	58
15.3.28.	Patiromer - VELTASSA (CAP) - EMEA/H/C/004180/X/0031/G	58
15.3.29.	Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0121.....	58
15.3.30.	Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0138.....	59
15.3.31.	Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0050	59
15.3.32.	Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0036	59
15.3.33.	Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0035	60
15.3.34.	Tepotinib - TEPMETKO (CAP) - EMEA/H/C/005524/II/0009	60
15.3.35.	Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/II/0006, Orphan.....	60

16. Annex I - Periodic safety update reports (PSURs) 60

16.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only.....	61
16.1.1.	Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HUKYNDRA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); LIBMYRIS (CAP); YUFLYMA (CAP) - PSUSA/00010783/202212	61
16.1.2.	Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202301	61
16.1.3.	Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202301	61
16.1.4.	Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202302	61
16.1.5.	Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202301	61
16.1.6.	Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202302.....	61
16.1.7.	Birch bark extract - FILSUEVZ (CAP) - PSUSA/00010446/202301	62
16.1.8.	Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202301	62
16.1.9.	Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202301	62
16.1.10.	Casirivimab, imdevimab (Ronapreve) - RONAPREVE (CAP) - PSUSA/00010963/202301....	62
16.1.11.	Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/202212	62
16.1.12.	Dapivirine - DAPIVIRINE VAGINAL RING 25 MG (Art 58) - EMEA/H/W/002168/PSUV/0021	62

16.1.13.	Daridorexant - QUVIVIQ (CAP) - PSUSA/00010993/202301	63
16.1.14.	Dasabuvir - EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010773/202301	63
16.1.15.	Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202301	63
16.1.16.	Eptacog beta (activated) - CEVENFACTA (CAP) - PSUSA/00011006/202301	63
16.1.17.	Eptifibatide - INTEGRILIN (CAP) - PSUSA/00001246/202301	63
16.1.18.	Faricimab - VABYSMO (CAP) - PSUSA/00011016/202301	63
16.1.19.	Finerenone - KERENDIA (CAP) - PSUSA/00010978/202301	63
16.1.20.	Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202302	64
16.1.21.	Glucagon - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202301	64
16.1.22.	Glucarpidase - VORAXAZE (CAP) - PSUSA/00010968/202301	64
16.1.23.	Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202301	64
16.1.24.	Inclisiran - LEQVIO (CAP) - PSUSA/00010904/202212	64
16.1.25.	Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202302	64
16.1.26.	Lixisenatide - LYXUMIA (CAP) - PSUSA/00010017/202301	64
16.1.27.	Lonococog alfa - AFSTYLA (CAP) - PSUSA/00010559/202301	65
16.1.28.	Melphalan flufenamide - PEPAXTI (CAP) - PSUSA/00011013/202302	65
16.1.29.	Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202301	65
16.1.30.	Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202301	65
16.1.31.	Omalizumab - XOLAIR (CAP) - PSUSA/00002214/202212	65
16.1.32.	Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202301	65
16.1.33.	Plerixafor - MOZOBIL (CAP) - PSUSA/00002451/202212	65
16.1.34.	Pneumococcal polysaccharide conjugate vaccine (15 valent, adsorbed) - VAXNEUVANCE (CAP) - PSUSA/00010975/202301	66
16.1.35.	Pneumococcal polysaccharide conjugate vaccine (10-valent, adsorbed) - SYNFLORIX (CAP) - PSUSA/00009262/202212	66
16.1.36.	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) - PREVENAR 13 (CAP) - PSUSA/00009263/202301 (with RMP)	66
16.1.37.	Quadrivalent influenza vaccine (recombinant, prepared in cell culture) - SUPEMTEK (CAP) - PSUSA/00010886/202301	66
16.1.38.	Ravulizumab - ULTOMIRIS (CAP) - PSUSA/00010787/202212	66
16.1.39.	Regdanvimab - REGKIRONA (CAP) - PSUSA/00010964/202302	66
16.1.40.	Remimazolam - BYFAVO (CAP) - PSUSA/00010924/202301	66
16.1.41.	Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202302	67
16.1.42.	Romosozumab - EVENITY (CAP) - PSUSA/00010824/202301	67
16.1.43.	Rufinamide - INOVELON (CAP) - PSUSA/00002671/202301	67
16.1.44.	Salmeterol, fluticasone propionate - BROPAIR SPIROMAX (CAP); SEFFALAIR SPIROMAX (CAP) - PSUSA/00010928/202301	67
16.1.45.	Sarilumab - KEVZARA (CAP) - PSUSA/00010609/202301	67

16.1.46.	Smallpox vaccine and monkeypox (live, modified vaccinia virus Ankara) - IMVANEX (CAP) - PSUSA/00010119/202301	67
16.1.47.	Sutimlimab - ENJAYMO (CAP) - PSUSA/00011023/202302.....	67
16.1.48.	Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202301.....	68
16.1.49.	Tecovirimat - TECOVIRIMAT SIGA (CAP) - PSUSA/00010971/202301.....	68
16.1.50.	Tipranavir - APTIVUS (CAP) - PSUSA/00002973/202212 (with RMP)	68
16.1.51.	Ustekinumab - STELARA (CAP) - PSUSA/00003085/202212	68
16.1.52.	Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202301	68
16.1.53.	Voclosporin - LUPKYNIS (CAP) - PSUSA/00011020/202301.....	68
16.1.54.	Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202212	68
16.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	69
16.2.1.	¹³ C-urea, ¹⁴ C-urea - HELICOBACTER TEST INFAI (CAP); PYLOBACTELL (CAP); NAP - PSUSA/00000006/202301	69
16.2.2.	Lenalidomide - LENALIDOMIDE ACCORD (CAP); LENALIDOMIDE KRKA (CAP); LENALIDOMIDE KRKA D.D. (SRD) (CAP); LENALIDOMIDE KRKA D.D. NOVO MESTO (CAP); LENALIDOMIDE MYLAN (CAP); REVLIMID (CAP); NAP - PSUSA/00001838/202212.....	69
16.2.3.	Oxybutynin - KENTERA (CAP); NAP - PSUSA/00002253/202207	69
16.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	69
16.3.1.	5-fluorouracil (NAP) - PSUSA/00010000/202301.....	69
16.3.2.	Allergen for therapy: Dactylis Glomerata L., Phleum Pratense L., Anthoxanthum Odoratum L., Lolium Perenne L., Poa Pratensis L. (NAP) - PSUSA/00010465/202212	69
16.3.3.	Aldesleukin (NAP) - PSUSA/00000076/202212	70
16.3.4.	Alitretinoin (NAP) - PSUSA/00010710/202301	70
16.3.5.	Amisulpride (NAP) - PSUSA/00000167/202301.....	70
16.3.6.	Atracurium (NAP) - PSUSA/00000267/202212	70
16.3.7.	Calcium chloride dihydrate, magnesium chloride hexahydrate, malic acid, sodium acetate trihydrate, sodium chloride, potassium chloride/calcium chloride dihydrate, sodium chloride, sodium lactate, potassium chloride/calcium chloride, sodium chloride, potassium chloride (NAP) - PSUSA/00010622/202301	70
16.3.8.	Cefprozil (NAP) - PSUSA/00000605/202212.....	70
16.3.9.	Cilostazol (NAP) - PSUSA/00010209/202301.....	71
16.3.10.	Cimicifuga racemosa (L.) Nutt., rhizoma (NAP) - PSUSA/00000755/202301.....	71
16.3.11.	Cisplatin (NAP) - PSUSA/00000778/202212	71
16.3.12.	Codeine camphosulphonate, sodium benzoate, codeine camphosulphonate, sulfogaiacol, grindelia soft extract (NAP) - PSUSA/00010542/202212	71
16.3.13.	Enalapril, nitrendipine (NAP) - PSUSA/00001213/202301	71
16.3.14.	Felodipine (NAP) - PSUSA/00001356/202212.....	71
16.3.15.	Furosemide (NAP) - PSUSA/00001491/202301.....	71
16.3.16.	Haemophilus influenzae, klebsiella ozaenae, klebsiella pneumoniae, moraxella catarrhalis, staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes, streptococcus viridans vaccine (NAP) - PSUSA/00001582/202212.....	72

16.3.17.	Hypericum perforatum L., herba (NAP) - PSUSA/00001701/202301.....	72
16.3.18.	Ibutilide (NAP) - PSUSA/00001713/202212.....	72
16.3.19.	Levobupivacaine (NAP) - PSUSA/00001848/202212.....	72
16.3.20.	Sertindole (NAP) - PSUSA/00002695/202301.....	72
16.3.21.	Tetanus vaccines (NAP) - PSUSA/00002910/202301.....	72
16.4.	Follow-up to PSUR/PSUSA procedures	72
16.4.1.	Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.3.....	72
16.4.2.	Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.3.....	73
16.4.3.	Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.3.....	73
16.4.4.	Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/LEG 021.....	73
16.4.5.	Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 063.....	73
16.5.	Variation procedure(s) resulting from PSUSA evaluation	74
16.5.1.	Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0063.....	74
16.6.	Expedited summary safety reviews	74
17.	Annex I – Post-authorisation safety studies (PASS)	74
17.1.	Protocols of PASS imposed in the marketing authorisation(s).....	74
17.1.1.	Fosdenopterin – NULIBRY (CAP) - EMEA/H/C/PSP/S/0103.1.....	74
17.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	74
17.2.1.	Birch bark extract - FILSUEZ (CAP) - EMEA/H/C/005035/MEA 001.1.....	74
17.2.2.	Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.7.....	75
17.2.3.	Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/MEA 007.2.....	75
17.2.4.	Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 006.2.....	75
17.2.5.	Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001.....	75
17.2.6.	Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58) - EMEA/H/W/002320/MEA 002.3.....	76
17.2.7.	Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 016.3.....	76
17.2.8.	Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 017.....	76
17.2.9.	Maribavir - LIVTENCITY (CAP) - EMEA/H/C/005787/MEA 005.....	76
17.2.10.	Niraparib, abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/MEA 001.....	76
17.2.11.	Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481/MEA 001.....	77
17.2.12.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.5.....	77
17.2.13.	Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 001.2.....	77
17.2.14.	Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 002.2.....	77
17.2.15.	Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.3.....	77
17.2.16.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 018.3.....	78
17.2.17.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 019.3.....	78
17.2.18.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 020.3.....	78
17.2.19.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 025.1.....	78

17.2.20.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.7	78
17.2.21.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 062.1	79
17.2.22.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 064.1	79
17.2.23.	Vutrisiran - AMVUTTRA (CAP) - EMEA/H/C/005852/MEA 002.1	79
17.3.	Results of PASS imposed in the marketing authorisation(s).....	80
17.3.1.	Chlormadinone acetate, ethinyl estradiol (NAP) - EMEA/H/N/PSR/J/0042	80
17.4.	Results of PASS non-imposed in the marketing authorisation(s).....	80
17.4.1.	Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0031	80
17.4.2.	Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/II/0032	80
17.4.3.	Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0034	80
17.4.4.	Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.14	81
17.4.5.	Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0070.....	81
17.4.6.	Radium (Ra ²²³) - XOFIGO (CAP) - EMEA/H/C/002653/II/0052	81
17.4.7.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0052.....	81
17.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	82
17.5.1.	Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 022	82
17.5.2.	Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/MEA 002.4.....	82
17.5.3.	Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - RIARIFY (CAP) - EMEA/H/C/004836/MEA 002	82
17.5.4.	Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRYDONIS (CAP) - EMEA/H/C/004702/MEA 002	82
17.5.5.	Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 005.1.....	83
17.5.6.	Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/MEA 006.3	83
17.5.7.	Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/MEA 029.4	83
17.5.8.	Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.12.....	83
17.5.9.	Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.6.....	83
17.5.10.	Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.2.....	84
17.5.11.	Lutetium (¹⁷⁷ Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.12.....	84
17.5.12.	Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.14	84
17.5.13.	Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.5.....	84
17.5.14.	Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.6.....	84
17.5.15.	Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001.3	85
17.5.16.	Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 002.4	85
17.5.17.	Sutimlimab - ENJAYMO (CAP) - EMEA/H/C/005776/MEA 003.....	85
17.5.18.	Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.7.....	85
17.6.	Others	85

17.6.1.	Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.3.....	85
17.6.2.	Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 018	86
17.6.3.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 009.1	86
17.6.4.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.3	86
17.7.	New Scientific Advice	86
17.8.	Ongoing Scientific Advice	86
17.9.	Final Scientific Advice (Reports and Scientific Advice letters)	87
18.	Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments	87
18.1.	Annual reassessments of the marketing authorisation	87
18.1.1.	Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/S/0010 (without RMP)	87
18.1.2.	Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/S/0004 (with RMP)	87
18.2.	Conditional renewals of the marketing authorisation	87
18.2.1.	Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0071 (without RMP)	87
18.2.2.	Loncastuximab tesirine - ZYNLONTA (CAP) - EMEA/H/C/005685/R/0009 (without RMP)....	87
18.2.3.	Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0042 (without RMP).....	88
18.2.4.	Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/R/0012 (without RMP).....	88
18.2.5.	Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/R/0035 (without RMP)...	88
18.3.	Renewals of the marketing authorisation	88
18.3.1.	Adalimumab - IDACIO (CAP) - EMEA/H/C/004475/R/0022 (without RMP)	88
18.3.2.	Bevacizumab - ZIRABEV (CAP) - EMEA/H/C/004697/R/0029 (without RMP)	88
18.3.3.	Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/R/0044 (without RMP)	88
18.3.4.	Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/R/0018 (without RMP)	88
18.3.5.	Macimorelin - GHRYVELIN (CAP) - EMEA/H/C/004660/R/0020 (without RMP)	89
18.3.6.	Miglustat - MIGLUSTAT DIPHARMA (CAP) - EMEA/H/C/004904/R/0019 (without RMP).....	89
18.3.7.	Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/R/0023 (without RMP)	89
18.3.8.	Pegfilgrastim - PELMEG (CAP) - EMEA/H/C/004700/R/0025 (without RMP).....	89
18.3.9.	Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/R/0039 (without RMP)	89
18.3.10.	Silodosin - SILODOSIN RECORDATI (CAP) - EMEA/H/C/004964/R/0012 (without RMP).....	89
19.	Annex II – List of participants	89
20.	Annex III - List of acronyms and abbreviations	98
21.	Explanatory notes	98

1. Introduction

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

The Chairperson opened the 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.

1.2. Agenda of the meeting on 28-31 August 2023

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

1.3. Minutes of the previous meeting on 03-06 July 2023

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

Post-meeting note: the PRAC minutes of the meeting held on 03-06 July 2023 were published on the EMA website on 21 September 2023 ([EMA/PRAC/397811/2023](#)).

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

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

Applicant(s): various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Krõõt Aab

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for pseudoephedrine-containing products following the assessment of the PSUR single assessment (PSUSA) procedure on ibuprofen/pseudoephedrine (PSUSA/00001711/202207) concluded in February 2023. The data submitted by the MAHs within the PSUSA procedure suggested a causal relationship between posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS) and pseudoephedrine use, based on the compatible and suggestive time to onset, the biological plausibility and the lack of alternative aetiologies for some patients without any risk factors. Considering the seriousness of PRES and RCVS, the overall safety profile of pseudoephedrine and the indications for which the medicines are approved, the matter was referred to PRAC for further evaluation. For further background, see [PRAC minutes January 2023](#), [PRAC minutes February 2023](#) and [PRAC minutes May 2023](#).

Summary of recommendation(s)/conclusions

- PRAC agreed on a draft list of experts for the ad-hoc expert group (AHEG) meeting scheduled to be held on 14 September 2023.

Post-meeting note: On 08 September 2023, the final list of experts for the AHEG meeting was adopted via written procedure.

3.3. Procedures for finalisation

3.3.1. Topiramate (NAP); topiramate, phentermine (NAP) - EMEA/H/A-31/1520

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for topiramate- and topiramate/phentermine-containing medicines is to be concluded. The procedure was initiated in 2022 following the publication by *Bjørk et al.*¹ in which the authors suggested an increased risk of neurodevelopmental disorders (NDD), in particular autism spectrum disorders (ASD) and intellectual disability (ID), in children with prenatal exposure to topiramate. Given the potential increased risk of NDD highlighted in this study with in utero exposure to topiramate and the known risk of congenital malformations, the matter was referred to PRAC for further evaluation. A final assessment of the data submitted was performed by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes September 2022](#), [PRAC minutes December 2022](#)², [PRAC minutes January 2023](#), [PRAC minutes February 2023](#), [PRAC minutes March 2023](#) and [PRAC minutes June 2023](#).

Discussion

PRAC discussed the conclusion reached by the Rapporteurs.

PRAC reviewed the totality of the data submitted during this review in relation to the risk of NDD and further reviewed new relevant data on the known risks of major congenital malformations (MCM) and foetal growth restriction. These data included the responses submitted in writing by the MAHs, available literature and the outcome of the consultation with the Scientific Advisory Group on Neurology ([SAG-N](#)).

PRAC confirmed the current knowledge that MCM and foetal growth restrictions are identified risks. PRAC also considered an increased risk of NDD including ASD, ID or attention deficit hyperactivity disorder (ADHD) in children of mothers with epilepsy exposed to topiramate in utero as possible, compared with children of mothers with epilepsy not exposed to an antiepileptic drug. However, no final conclusion could be drawn at this stage because available relevant data from epidemiological studies (*Bjørk et al.*, 2022¹; *Dreier et al.*,

¹ Bjørk M, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. *JAMA Neurol*. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

² Held on 28 November – 01 December 2022

2023³, Hernandez-Diaz S et al., 2022⁴) on this matter show inconsistent results. Therefore, NDD should be considered an important potential risk for topiramate use during pregnancy.

In view of the new potential risk of NDD and the known risks of MCM and foetal growth restrictions, PRAC concluded that there is a need to implement further risk minimisation measures (RMMs) in the form of a pregnancy prevention programme to reduce in utero exposure to topiramate. While PRAC confirmed the contraindications in pregnancy and in women of childbearing potential (WCP) not using highly effective contraception in the indications of migraine and treatment of overweight, the Committee also recommended the implementation of contraindications in the epilepsy indication. In epilepsy, PRAC agreed that the contraindication is applicable for pregnant women unless there is no suitable alternative treatment as well as for women of childbearing potential not using highly effective contraception. However, for the latter group, an exception is included for women for whom there is no suitable alternative but who plan a pregnancy and who are fully informed about the risks of taking topiramate during pregnancy.

PRAC also recommended additional RMMs comprising of a patient card and educational materials as a healthcare professional guide including a risk awareness form and a patient guide in order to increase awareness of healthcare professionals and patients on the risks of adverse outcomes after in utero exposure to topiramate, and on measures to be taken to minimise these risks. A warning on the outer packaging was also recommended.

Moreover, the MAHs of topiramate mono-component products should conduct post-authorisation studies including a drug utilisation study to evaluate the effectiveness of the measures implemented, and a survey to assess the level of knowledge of healthcare professionals and patients on the risks and minimisation measures implemented as an outcome of this review.

As a consequence, PRAC considered that the benefit-risk balance of all topiramate-containing products remains favourable subject to the agreed conditions to the marketing authorisations, the agreed amendments to the product information and the risk minimisation measures mentioned above.

Summary of recommendation(s)/conclusions

- PRAC adopted a recommendation to vary⁵ the terms of the marketing authorisations for topiramate-containing medicines to be considered by CMDh for adoption of a position.
- PRAC agreed on the distribution of a direct healthcare professional communication ([DHPC](#)) together with a communication plan.

Post-meeting note 1: the press release entitled 'PRAC recommends new measures to avoid topiramate exposure in pregnancy' ([EMA/384677/2023](#)) was published on the EMA website on 01 September 2023.

Post-meeting note 2: On 18 October 2023, the assessment report ([EMA/443729/2023](#)) for the procedure was published on the EMA website.

³ Dreier JW, Bjørk M, Alvestad S, et al., 'Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders', *JAMA Neurol*. Published online April 17, 2023. doi: 10.1001/jamaneurol.2023.0674. Online ahead of print. PMID: 37067807

⁴ Hernandez-Diaz S, Straub L, Bateman B, et al., Topiramate During Pregnancy and the Risk of Neurodevelopmental Disorders in Children. (2022), In: ABSTRACTS of ICPE 2022, the 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Copenhagen, Denmark, 26–28 August, 2022. *Pharmacoepidemiol Drug Saf*, 2022; 31 Suppl 2:3-678, abstract 47

⁵ Update of SmPC sections 4.2, 4.3, 4.4, 4.5 and 4.6. The labelling and package leaflet are updated accordingly.

3.4. Re-examination procedures⁶

None

3.5. Others

None

4. Signals assessment and prioritisation⁷

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Nivolumab – OPDIVO (CAP), OPDUALAG (CAP)

Applicant(s): Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Signal of pancreatic failure

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 pancreatic failure was identified by the Norwegian Medicines Agency (NOMA), based on 8 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance and the literature, PRAC considered that further evaluation on the signal of pancreatic failure for Opdivo (nivolumab) and Opdualag (nivolumab) is warranted and agreed to extend the signal to other active substances of the class of immune-checkpoint inhibitors, including Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), and tremelimumab-containing products Imjudo and Tremelimumab AstraZeneca.

PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for the nivolumab-containing products Opdivo and Opdualag, for Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab),

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

⁷ 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

Yervoy (ipilimumab), and for the tremelimumab-containing products Imjudo and Tremelimumab AstraZeneca should submit to EMA, within 60 days, a cumulative review of cases of pancreatic failure from all sources including clinical studies, spontaneous reports and literature, as well as a discussion on possible biological plausibility and mechanism of this association.

- PRAC will assess the cumulative review within a 90-day timetable.

4.2. New signals detected from other sources

4.2.1. Ipilimumab – YERVOY (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of coeliac disease

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 coeliac disease was identified by EMA, based on cases identified in the literature. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in literature and EudraVigilance, PRAC agreed that further evaluation on the signal of coeliac disease for Yervoy (ipilimumab) is warranted and agreed to extend the signal to other active substances of the class of immune-checkpoint inhibitors, including Opdivo (nivolumab), Opdualag (nivolumab), Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), Yervoy (ipilimumab), and tremelimumab-containing products Imjudo and Tremelimumab AstraZeneca.

Summary of recommendation(s)

- The MAHs for ipilimumab (Yervoy), the nivolumab-containing products Opdivo and Opdualag, Keytruda (pembrolizumab), Imfinzi (durvalumab), Bavencio (avelumab), Tecentriq (atezolizumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Tevimbra (tislelizumab), and tremelimumab-containing products Imjudo and Tremelimumab AstraZeneca should submit to EMA, within 60 days, a cumulative review of all cases of coeliac disease and related terms, including a review of the published literature, data from spontaneous reports and reports from studies, as well as a discussion on possible biological plausibility and mechanism of this association. The MAHs should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) as warranted.
- PRAC will assess the cumulative review within a 90-day timetable.

4.3. Signals follow-up and prioritisation

4.3.1. Acetazolamide (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of choroidal effusion and choroidal detachment

EPITT 19924 – follow up to April 2023

Background

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

The MAH of the originator acetazolamide-containing products replied to the request for information on the signal of choroidal effusion and choroidal detachment and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from case reports in EudraVigilance and literature and the MAH's responses, PRAC agreed that there is sufficient evidence to establish a causal relationship between treatment with acetazolamide and choroidal effusion and choroidal detachment and to add choroidal effusion and choroidal detachment as a warning and as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAHs for acetazolamide containing products should submit to EMA, within 60 days, a variation to amend⁸ the product information.

For the full PRAC recommendation, see [EMA/PRAC/359902/2023](#) published on 25 September 2023 on the EMA website.

4.3.2. Megestrol (NAP)

Applicant(s): various

PRAC Rapporteur: Eamon O'Murchu

Scope: Signal of meningioma

EPITT 19923 – follow up to April 2023

Background

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

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

Discussion

⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

Having considered the available evidence in EudraVigilance, literature and the responses of the MAHs, PRAC agreed that the current evidence is insufficient to establish a causal relationship between treatment with megestrol and meningioma.

Summary of recommendation(s)

- In the next PSUR⁹, the MAH(s) for megestrol-containing products should monitor cases of meningioma, and discuss any new case reports and literature on this topic.

See [EMA/PRAC/359902/2023](https://www.ema.europa.eu/en/press-room/2023/09/23-09-23-ema-prac-359902-2023) published on 25 September 2023 on the EMA website.

4.4. Variation procedure(s) resulting from signal evaluation

None

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Arpraziquantel - EMEA/H/W/004252

Scope: Treatment of schistosomiasis in children

5.1.2. Elranatamab - EMEA/H/C/005908, PRIME, Orphan

Applicant: Pfizer Europe MA EEIG

Scope: Treatment of adult patients with relapsed or refractory multiple myeloma

5.1.3. Exagamglogene autotemcel - EMEA/H/C/005763, PRIME, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited, ATMP

Scope: Treatment of transfusion-dependent β -thalassemia and sickle cell disease

5.1.4. Fidanacogene elaparvovec - EMEA/H/C/004774, PRIME, Orphan

Applicant: Pfizer Europe MA EEIG, ATMP

Scope: Treatment of severe and moderately severe haemophilia B

⁹ Data lock point 17 August 2025

5.1.5. Germanium (⁶⁸Ge) chloride, gallium (⁶⁸Ga) chloride - EMEA/H/C/006053

Scope: Indicated for in vitro radiolabelling of specific carrier molecules to be used for positron emission tomography (PET) imaging

5.1.6. Leriglitazone - EMEA/H/C/005757, Orphan

Applicant: Minoryx Therapeutics S.L.

Scope: Treatment of cerebral progression and myelopathy in male patients with adrenoleukodystrophy (ALD)

5.1.7. Momelotinib - EMEA/H/C/005768, Orphan

Applicant: Glaxosmithkline Trading Services Limited

Scope: Treatment of disease-related splenomegaly or symptoms and anaemia

5.1.8. Rozanolixizumab - EMEA/H/C/005824, Orphan

Applicant: UCB Pharma

Scope: Treatment of generalised myasthenia gravis (gMG)

5.1.9. Tofersen - EMEA/H/C/005493, Orphan

Applicant: Biogen Netherlands B.V.

Scope: Treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene

5.1.10. Ustekinumab - EMEA/H/C/006101

Scope: Treatment of plaque psoriasis, arthritis psoriatic, Crohn's Disease and ulcerative colitis

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

See also Annex I 15.2.

5.2.1. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/II/0006

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of substantial updates to the protocol of study SIGA-246-021 listed as a specific obligation in the Annex II of the product information in order to reflect the transfer of sponsorship from SIGA Technologies, Inc. to the NIH Division of Microbiology and Infection Disease protocol. This is a phase 4, observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease. The Annex II and the RMP submitted version 1.2 are updated accordingly

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.

PRAC is evaluating a type II variation procedure for Tecovirimat Siga, a centrally authorised medicine containing tecovirimat, to update the RMP due to substantial updates to the protocol of SIGA-246-021 study listed as a specific obligation in the Annex II of the product information in order to reflect the transfer of sponsorship from SIGA Technologies, Inc. to the NIH Division of Microbiology and Infection Disease protocol. 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. For further background, see [PRAC minutes April 2023](#) and [PRAC minutes May 2023](#).

Summary of advice

- The RMP for Tecovirimat Siga (tecovirimat) in the context of the variation procedure under evaluation by PRAC and CHMP could be considered acceptable provided that an update to RMP version 1.4 is submitted.
- In view of the protocol updates submitted, the MAH should update the study design from non-interventional to interventional in Annex II-D. Furthermore, PRAC supported that the study should be categorised as PAES instead of a PASS, considering that safety is considered a secondary objective in the amended protocol.

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

See also Annex I 15.3.

5.3.1. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0133

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Submission of the final report from study CSTI571I2201 - A European observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ acute lymphocytic leukaemia (ALL) patients treated with chemotherapy plus imatinib and with or without haematopoietic stem cell transplantation (HSCT), listed as an obligation in the Annex II of the product information. This study has been designed as an observational, multi-centre registry to collect efficacy and safety data in Ph+ ALL paediatric patients (ages 1 to <18 years old) treated with chemotherapy plus imatinib, with or without HSCT, primarily in European countries. The Annex II and the RMP (version 13.0) are updated accordingly

Background

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

CHMP is evaluating a type II variation for Glivec, a centrally authorised product containing imatinib, to amend the product information (PI), Annex II and the RMP following submission of the final report of CSTI571I2201 study, listed as an obligation in Annex II-D. PRAC is

responsible for providing advice to CHMP on the necessary updates to the RMP to support this procedure. For further background, see [PRAC minutes May 2023](#).

Summary of advice

- The RMP version 13.0 for Glivec (imatinib) in the context of the variation under evaluation by CHMP is considered acceptable.
- PRAC considered that the obligation for conducting the study was fulfilled and agreed to remove the category 1 study from Annex II-D of the product information. Consequently, the study should be removed from the RMP and 'paediatric patients: long-term follow-up' as missing information should be removed from the list of safety concerns. PRAC also agreed with the removal of the additional monitoring status and consequently the black triangle and additional monitoring statements from the product information.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. (1r,2s,5s)-n-{{(1s)-1-cyano-2-[(3s)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3- [3-methyl-n-(trifluoroacetyl)-l-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide / ritonavir (Paxlovid) - PAXLOVID (CAP) - PSUSA/00010984/202212

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Paxlovid, a centrally authorised medicine containing (1r,2s,5s)-n-{{(1s)-1-cyano-2-[(3s)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3- [3-methyl-n-(trifluoroacetyl)-l-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide/ritonavir 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 Paxlovid in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the current information on the undesirable effect 'dysgeusia' in the package leaflet. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁰.
- In the next PSUR, the MAH should provide cumulative reviews of cases of eye disorders,

¹⁰ Update of section 4 of the package leaflet. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

co-administration of Paxlovid with immunosuppressants, changes in lipids (hypercholesterolaemia and hypertriglyceridaemia), hyperglycaemia/diabetes mellitus, confusional state, renal disorders, bleeding events including heavy menstrual bleeding and haemorrhagic diarrhoea, pancreatitis, hepatobiliary disorders, Stevens-Johnson syndrome and toxic epidermal necrolysis.

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.

6.1.2. Abatacept - ORENCIA (CAP) - PSUSA/00000013/202212

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Orencia, a centrally authorised medicine containing abatacept 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 Orencia (abatacept) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 90 days, an updated cumulative review of cases of progressive multifocal leukoencephalopathy (PML), including data from post-marketing setting, clinical trials and literature, along with a causality assessment taken into account WHO causality criteria and the publication *Segec et al.* for the strategy in regulatory decision-making for management of PML. In addition, the MAH should submit to EMA a cumulative review of cases of sarcoidosis, including data from post-marketing setting, clinical trials and literature, along with a causality. Finally, the MAH should discuss the need for an update of the product information and/or other regulatory actions as appropriate.

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. Brexucabtagene autoleucel - TECARTUS (CAP) - PSUSA/00010903/202301

Applicant: Kite Pharma EU B.V., ATMP

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Tecartus, a centrally authorised medicine containing brexucabtagene autoleucl 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 Tecartus (brexucabtagene autoleucl) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add infusion related reaction as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹¹.
- In the next PSUR, the MAH should provide cumulative reviews of cases status epilepticus and of immune effector cell-associated neurotoxicity syndrome (ICANS) and propose 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.

6.1.4. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202301

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of 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.
- The current terms of the marketing authorisation(s) should be maintained.

¹¹ 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

- In the next PSUR, the MAH should provide a detailed analysis of cases of drug-induced liver injury (DILI), including data from post-marketing setting and from clinical trials. In addition, the MAH should discuss whether the product information should be amended based on the data regarding cases of hot flushes, thromboembolic events, renal and urinary disorders, infections of the urinary tract and gastrointestinal disorders.

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

6.1.5. [Dolutegravir - TIVICAY \(CAP\); dolutegravir, abacavir, lamivudine - TRIUMEQ \(CAP\); dolutegravir, lamivudine - DOVATO \(CAP\) - PSUSA/00010075/202301](#)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Tivicay, Dovato and Triumeq, centrally authorised medicines containing dolutegravir, dolutegravir/lamivudine, dolutegravir/abacavir/lamivudine respectively and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tivicay (dolutegravir), Dovato (dolutegravir/lamivudine) and Triumeq (dolutegravir/abacavir/lamivudine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of abacavir-containing products, i.e. Triumeq (dolutegravir/abacavir/lamivudine), should be updated to include cardiovascular events as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied¹².
- In the next PSURs, the MAH should closely monitor the following safety concerns listed in the PSUR: hypersensitivity reactions, hepatobiliary reactions, depression including suicidal ideation and behaviours, serious rash and neural tube defects, as well as use in pregnancy, use in elderly and long term safety. The MAH should also provide an assessment of new cases of anaphylaxis, severe cutaneous adverse reaction (SCARs), thrombocytopenia, myocarditis, hyperglycaemia and diabetes mellitus, and holoprosencephaly or midline defects.

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.

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

6.1.6. Ibritumomab tiuxetan - ZEVALIN (CAP) - PSUSA/00001704/202302

Applicant: Ceft Biopharma s.r.o.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

PRAC is currently reviewing the benefit-risk balance of Zevalin (ibritumomab tiuxetan), in the framework of the assessment of a PSUR single assessment (PSUSA) procedure.

Summary of recommendation(s) and conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the November 2023 PRAC meeting, where further discussion and adoption of a recommendation is planned.

6.1.7. Relugolix - ORGOVYX (CAP) - PSUSA/00010994/202301

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Orgovyx, a centrally authorised medicine containing relugolix 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 Orgovyx (relugolix) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include urticaria and angioedema as undesirable effects with a frequency 'uncommon'. 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.

¹³ 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

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. Abacavir - ZIAGEN (CAP); NAP - PSUSA/00000010/202212

Applicant: ViiV Healthcare B.V. (Ziagen), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Abacavir is a nucleoside reverse transcriptase inhibitor indicated for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children, in antiretroviral combination therapy.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cardiovascular events as a warning. Therefore, the current terms of the marketing authorisations 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.

6.2.2. Abacavir, lamivudine - KIVEXA (CAP); NAP - PSUSA/00000011/202212

Applicant: ViiV Healthcare B.V. (Kivexa), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors indicated in antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Kivexa, a centrally authorised medicine containing abacavir/lamivudine, and nationally authorised

¹⁴ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

medicines containing abacavir/lamivudine and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir/lamivudine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cardiovascular events as a warning. Therefore, the current terms of the marketing authorisations should be varied¹⁵.

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.

6.2.3. Abacavir, lamivudine, zidovudine - TRIZIVIR (CAP); NAP - PSUSA/00003144/202212

Applicant: ViiV Healthcare B.V. (Trizivir), various

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

Background

Abacavir, lamivudine and zidovudine are nucleoside reverse transcriptase inhibitors indicated for the treatment of human immunodeficiency virus (HIV) infection in adults, under certain conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Trizivir, a centrally authorised medicine containing abacavir/lamivudine/zidovudine, and nationally authorised medicines containing abacavir/lamivudine/zidovudine and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abacavir/lamivudine/zidovudine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include cardiovascular events as a warning. Therefore, the current terms of the marketing authorisations 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.

¹⁵ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

¹⁶ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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

See also Annex I 16.3.

6.3.1. Acebutolol (NAP) - PSUSA/00000018/202212

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

Background

Acebutolol is a cardioselective beta-blocker indicated in the management of hypertension, angina pectoris, cardiac rhythm disturbances and post myocardial infarction, subject to specified conditions.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing acebutolol 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 acebutolol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the risk of giving birth to small-for-gestational-age newborns following the use of acebutolol during pregnancy and to add alopecia as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.

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

6.3.2. Gemcitabine (NAP) - PSUSA/00001519/202301

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Gemcitabine is a nucleoside analogue indicated for the treatment of treatment of non-small cell lung cancer, pancreatic cancer, urothelial cancer (bladder, renal pelvis, ureter, and urethra), breast cancer, ovarian cancer, cervical cancer, and biliary tract cancer.

¹⁷ Update of SmPC sections 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing gemcitabine 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 gemcitabine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include severe cutaneous adverse drug reactions as a warning and to add acute generalised exanthematous pustulosis 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 Hikma should provide a cumulative review of cases of cardiomyopathy and of retinopathy. In addition, the MAHs for the originator and hybrid gemcitabine-containing products should submit a comprehensive review of cases of pulmonary arterial hypertension pulmonary hypertension, including data from clinical trials, post marketing and literature sources and discuss whether an update of product information is warranted.

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

6.3.3. Paroxetine (NAP) - PSUSA/00002319/202212

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) indicated for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder, social anxiety disorder (SAD)/social phobia, generalised anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and premenstrual dysphoric disorder (PMDD).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing paroxetine 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 paroxetine-containing medicinal products in the approved indication(s) remains unchanged.

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 CMDh for adoption of a position

- Nevertheless, the product information should be updated to add leukopenia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.
- In the next PSUR, the brand leader MAH for paroxetine-containing medicinal products should submit cumulative reviews of cases of cough and of interstitial lung disease, including data from clinical trials, post-marketing setting and literature, and discuss whether an update of the product information is warranted.

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

6.4. Follow-up to PSUR/PSUSA procedures

See Annex I 16.4.

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews²⁰

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)²¹

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)²²

See also Annex I 17.2.

7.2.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 012

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for study BO44691: PASS to evaluate the long-term safety of Hemlibra in patients with moderate Haemophilia A and severe bleeding phenotype

Background

¹⁹ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of a position

²⁰ 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

²¹ In accordance with Article 107n of Directive 2001/83/EC

²² 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

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.

As part of the RMP for Hemlibra (emicizumab) the MAH was required to conduct a category 3 study in order to characterise the important potential risk of thromboembolic (TE) events (not associated with activated prothrombin complex concentrate (aPCC) exposure) specifically and inform on the long-term safety profile of emicizumab in patients with moderate hemophilia A (HA) (FVIII \geq 1% and \leq 5%) and severe bleeding phenotype. The MAH submitted a protocol version 1.0 for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

Summary of advice

- The study protocol for Hemlibra (emicizumab) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to EMA before finalisation of the procedure.
- The MAH should provide clarifications on the milestones, secondary objectives, variables and data source, as well as to provide further details about the statistical analysis plan.
- A 60-day timetable will be followed.

7.3. Results of PASS imposed in the marketing authorisation(s)²³

See also Annex I 17.3.

7.3.1. Roflumilast – DAXAS (CAP) - EMEA/H/C/PSR/S/0041

Applicant: AstraZeneca AB

PRAC Rapporteur: Monica Martinez Redondo

Scope: Final study report for a long-term post-marketing observational study of the safety of roflumilast

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.

Daxas, a centrally authorised medicine containing roflumilast, was authorised in 2010. At the time of granting the marketing authorisation, the MAH was imposed to conduct a PASS ([Annex II-D](#)) to evaluate the long-term safety of Daxas (roflumilast) in the treatment of chronic obstructive pulmonary disease (COPD).

The final study report was submitted to EMA by the MAH AstraZeneca AB on 21 December 2022. PRAC discussed the final study results and is responsible for evaluating them.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the PASS and the Rapporteur's assessment, PRAC considered that the obligation to perform the PASS is fulfilled.

²³ In accordance with Article 107p-q of Directive 2001/83/EC

- PRAC recommended to vary the terms of the marketing authorisation(s) by removing the study requirement from the conditions with regard to the safe and effective use of the medicinal product (Annex II-D) and by removing the additional monitoring status and consequently the black triangle and additional monitoring statements from the product information.

7.3.2. Valproate²⁴ (NAP) - EMEA/H/N/PSR/J/0036

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Survey among HCP to assess knowledge of HCP and behaviour with regards to PPP as well as receipt/use of DHPC and educational materials and survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials

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.

The MAH Sanofi-Aventis Recherche & Développement, on behalf of a consortium, submitted to EMA the final results version 1.0 of the 'surveys among HCP and patients to assess their knowledge and behaviour with respect to the new risk minimisation measures (RMM) for valproate use in Europe'. For further background, see [PRAC minutes November 2021](#)²⁵, [PRAC minutes June 2022](#), [PRAC minutes November 2022](#)²⁶, [PRAC minutes January 2023](#) and [PRAC minutes March 2023](#).

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'Survey among healthcare professionals (HCP) to assess knowledge of HCP and behaviour with regards to pregnancy prevention programme (PPP) as well as receipt/use of DHPC and educational materials' and 'Survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials', other (interim) available studies, data from literature, the outcome of the stakeholder's meeting held in February 2023 and the MAH's responses to the request for supplementary information (RSI), PRAC considered that the obligation to conduct the PASS is fulfilled.
- PRAC agreed with the update of the product information in the form of a boxed presentation of the contraindications for use during pregnancy to emphasize the different contraindication per indication, considering the knowledge deficiency in this area among psychiatrists observed in the results of the HCP Survey, and the confusion among general practitioners (GPs) regarding the contraindications for pregnancy observed in literature. No changes to the package leaflet (PL) are proposed. It is advised that any proposal to update the PL to improve readability is substantiated by a user test. PRAC also endorsed the content of the (new) 'core version of the HCP guide' and the (revised) 'core version of the patient guide'.

²⁴ Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

²⁵ Held on 25-28 October 2021

²⁶ Held on 24-27 October 2022

- The core version of the patient card agreed with the Article 31 referral concluded in 2018 remains valid. The annual risk acknowledgment form (ARAF) should be used and documented at initiation and during each annual review of treatment by a specialist. The core version agreed with the Article 31 referral concluded in 2018 remains valid. The MAH(s) should distribute revised version of the HCP guide, the revised patient guide and the ARAF in each EU member state (MS), in agreement with the national competent authority (NCA), together with a cover letter to explain the reason for distribution of such revised materials. To promote access and awareness of valproate and related active substances additional risk minimization measures (RMM) and PPP in each EU MS, the MAH(s) should ensure easy access to digital/electronic versions of the educational materials in the local language, with and without a QR code included in the packaging material and/or the PL.
- However, PRAC agreed that the need for further measures, as well as additional studies to investigate effectiveness of measures taken so far, will be determined after assessment of the final results of the ongoing joint drug utilisation study (DUS) (EMA/H/N/PSP/J/0075), when a complete picture on RMM effectiveness has become available. Nevertheless, the MAHs should already propose improvements of the additional RMM based on the findings of the survey.
- In addition, the MAH(s) should submit an updated risk management plan (RMP) after finalisation of this PASS procedure in accordance with the measures mentioned above. Furthermore, a qualitative study should be included in the RMP as category 3 study, in order to investigate barriers and reasons why certain measures part of the PPP are not always followed in clinical practice and the preferred ways of HCPs and patients to receive information on the PPP. The protocol for this study should be submitted by the innovator MAH. The MAHs of generic valproate-containing products can cross-refer to the study protocol to be submitted by the innovator in their RMPs.

7.4. Results of PASS non-imposed in the marketing authorisation(s)²⁷

See also Annex I 17.4.

7.4.1. Dimethyl fumarate - TECFIDERA (CAP) - EMA/H/C/002601/II/0082

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on results from study 109MS402 - Tecfidera (dimethyl fumarate) Pregnancy Exposure Registry, listed as a category 3 study in the RMP; this is an observational study and aims to address the safety concern of effects on pregnancy outcome and prospectively evaluates pregnancy outcomes in women with MS who were exposed to a Registry-specified Biogen MS product during the eligibility window for that product. The package leaflet is updated accordingly. The RMP version 15.1 has also been submitted. In addition, the MAH has taken the opportunity to introduce editorial changes to the product information

Background

²⁷ 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

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.

As stated in the RMP of Tecfidera (dimethyl fumarate), the MAH conducted a non-imposed non-interventional category 3 PASS 109MS402 - Tecfidera (dimethyl fumarate) Pregnancy Exposure Registry (TecGistry) to address the important potential risk of 'effects on pregnancy outcome' by assessing pregnancy and infant outcomes in participants with multiple sclerosis (MS) who were exposed to an MS product (of the MAH) listed in the registry during the eligibility period. The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see [PRAC minutes May 2023](#).

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that further information was necessary before the ongoing variation assessing the final study report can be recommended for approval. In particular, the MAH should further comment on the proposed amendments to the product information in line with PRAC's comments.
- A 30-day assessment timetable will be followed.

7.4.2. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0100

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 4.6 of the SmPC in order to update information on pregnancy based on the final synoptic report from study CNTO1275PSO4037 (OTIS); this is a pregnancy exposure registry for Stelara. The package leaflet is updated accordingly. The RMP version 26.2 has also been submitted

Background

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

Following assessment of the final report from study CNTO1275PSO4007 (pregnancy research initiative - exposure to ustekinumab during pregnancy: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers, final report assessed in EMEA/H/C/000958/II/0091), PRAC requested the MAH to submit the final report from the OTIS STELARA pregnancy exposure registry with an updated cumulative review of use in pregnancy, including a specific analysis of cardiac malformation. The Rapporteur assessed the MAH's final study report. For further background see [PRAC minutes November 2022](#)²⁸.

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be considered acceptable

²⁸ Held on 24-27 October 2022

provided that the MAH submits satisfactory responses to a request for supplementary information (RSI). In particular, the MAH should provide cumulative reviews of cases of spontaneous abortion and intrauterine death and stillbirth, and should further comment on the proposed amendments to the product information in line with PRAC's comments.

- A 60-day assessment timetable will be followed.

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

See also Annex I 17.5.

7.5.1. Zanamivir - DECTOVA (CAP) - EMEA/H/C/004102/MEA 003.2

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual update on the observational pregnancy registry study 201840 (listed as category 3 study in the RMP)

Background

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

The MAH had committed to perform a category 3 PASS to gain further understanding on safety following use of intravenous (IV) zanamivir during pregnancy (study 208140 - phase IV pregnancy registry study). Interim results for this study were submitted by the MAH and assessed by the Rapporteur for PRAC review.

Summary of advice

- Taking into account the low exposure outside of the setting of an influenza pandemic and that no patient was enrolled in the pregnancy registry study within a reasonable timeframe, PRAC agreed with the MAH's proposal to remove this category 3 study from the RMP. However, the safety concern 'safety in pregnancy' should be kept as missing information in the RMP. Moreover, following the removal of this study from the RMP, the MAH should propose additional pharmacovigilance activities where any new health data sources should be used to capture additional information on clinical safety in pregnancy.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

None

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

None

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of PRAC

12.1.1. PRAC membership

None

12.1.2. Vote by proxy

None

12.1.3. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals – Q2 2023

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see PRAC minutes May 2016 and PRAC minutes June 2018) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see PRAC minutes June 2016 and PRAC minutes June 2018), the EMA Secretariat updated PRAC on the quantitative measures collected for Q1 2023 of PRAC meetings. For previous update, see [PRAC minutes May 2023](#).

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 characteristics of the post-COVID-19 condition and post-acute sequelae of COVID-19, on the new SARS-CoV-2 variants, as well as on the study results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA vaccines) against the new SARS-CoV-2 variants.

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

12.7.1. PRAC work plan 2023 – update

The EMA Secretariat presented to PRAC a mid-year status update on the activities described in the [PRAC work plan 2023](#). PRAC will initiate its work plan for 2024 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, Heads of Medicines Agencies (HMA) and EU network.

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - quarterly workload measures and performance indicators – Q2 2023 and predictions

The EMA Secretariat presented to PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes May 2023](#).

12.8.2. PRAC workload statistics – Q2 2023

The EMA secretariat presented to PRAC the quarterly and cumulative figures to estimate the evolution of the PRAC workload for Q2 2023, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes May 2023](#).

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

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

Post-meeting note: following the PRAC meeting of September 2023, the updated EURD list was adopted by CHMP and CMDh 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

12.14. 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

12.14.3. Risk management plan (RMP) of medicinal product(s) – update on the process of publication on EMA website

The EMA Secretariat presented PRAC the final process of publication of full RMPs on EMA website, following the comments received from the Member States. For further background, see [PRAC minutes April 2023](#) and [PRAC minutes May 2023](#). The process, which includes identification and redaction of commercial confidential information/protected personal data, will start in October 2023 and will be applied for all types of procedures (with slight modifications for type IB variations). PRAC noted the information.

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. Revised process for prioritisation and regulatory follow-up of impact research (Rev.2)

The revised process for prioritisation and regulatory follow-up of impact research commissioned under the remit of the PRAC Strategy on measuring the impact of pharmacovigilance activities (revision 2.1) was endorsed by PRAC via written procedure on 05 September 2023. For further background, see [PRAC minutes July 2023](#).

12.21. Others

12.21.1. Guideline on clinical investigation of recombinant and human plasma-derived factor IX products and core SmPC – revision

The Haematology Working Party has finalised the revision of the Guideline on clinical investigation of recombinant and human plasma-derived factor IX products and core SmPC, following the public consultation in 2019 (for further information, see [Q&A revision of the FVIII and FIX guidelines \(europa.eu\)](#)). PRAC members were invited to provide their comments on the guideline in writing by 11 September 2023.

12.21.2. Patient Experience Data (PED) – priority activities and actions

The topic was postponed for the next plenary meeting.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation²⁹

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 timetables³⁰.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Amphotericin B (NAP)

Applicant: various

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Signal of hyperkalaemia

EPITT 19966 – New signal

Lead Member State(s): ES

14.1.2. Avatrombopag – DOPTELET (CAP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Monica Martinez Redondo

Scope: Signal of antiphospholipid syndrome

EPITT 19954 – New signal

Lead Member State(s): ES

14.1.3. Cefotaxime (NAP)

Applicant: various

PRAC Rapporteur: Jan Neuhauser

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

EPITT 19960 – New signal

²⁹ 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

³⁰ 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): AT

14.1.4. Cobimetinib – COTELLIC (CAP); Vemurafenib – ZELBORAF (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of aphthous ulcer, mouth ulceration, stomatitis

EPITT 19961 – New signal

Lead Member State(s): SE

14.1.5. Minoxidil³¹ (NAP)

Applicant: various

PRAC Rapporteur: Eamon O'Murchu

Scope: Signal of hypertrichosis in children following accidental exposure via patients

EPITT 19951 – New signal

Lead Member State(s): IE

14.1.6. Osimertinib – TAGRISSO (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of anaphylactic reaction

EPITT 19959 – New signal

Lead Member State(s): NL

14.1.7. Palbociclib – IBRANCE (CAP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of rhabdomyolysis by interaction with statins

EPITT 19963 – New signal

Lead Member State(s): DK

14.2. New signals detected from other sources

None

³¹ Topical formulation(s) only

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. Azacitidine - EMEA/H/C/006154

Scope: Treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML)

15.1.2. Eribulin - EMEA/H/C/006134

Scope: Treatment of breast cancer and liposarcoma

15.1.3. Ibuprofen - EMEA/H/C/006129

Scope: Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age

15.1.4. Paclitaxel - EMEA/H/C/006173

Scope: Treatment of metastatic breast cancer

15.1.5. Ranibizumab - EMEA/H/C/006055

Scope: Treatment of neovascular age-related macular degeneration (AMD)

15.1.6. Zoonotic influenza vaccine (h5n1) (surface antigen, inactivated, adjuvanted) - EMEA/H/C/006375

Scope: Active immunisation against H5 subtype of Influenza A virus

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. Acridinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS2548/0051; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS2548/0052

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of RMP version 8.1 to update the milestone for PASS study

D6560R00004 regarding Arrhythmia final report from 1H 2023 to 2H 2023

15.2.2. [Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR \(CAP\) - EMEA/H/C/003969/WS2546/0039; DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/WS2546/0040](#)

Applicant: Covis Pharma Europe B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of RMP version 5.1 to update the milestone for PASS study D6560R00004 regarding Arrhythmia final report from 1H 2023 to 2H 2023

15.2.3. [Baricitinib - OLUMIANT \(CAP\) - EMEA/H/C/004085/II/0043](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

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

15.2.4. [Emtricitabine, tenofovir disoproxil - EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA \(CAP\) - EMEA/H/C/004137/WS2486/0025](#)

Applicant: Zentiva k.s.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP version 5.1 for Emtricitabine/Tenofovir disoproxil in line with the reference medicinal product Truvada (EMEA/H/C/WS2320)

15.2.5. [Ertugliflozin, metformin hydrochloride - SEGLUROMET \(CAP\) - EMEA/H/C/004314/WS2537/0021; Ertugliflozin - STEGLATRO \(CAP\) - EMEA/H/C/004315/WS2537/0020; Ertugliflozin, sitagliptin - STEGLUJAN \(CAP\) - EMEA/H/C/004313/WS2537/0024](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP version 2.2 to update the final study report date for Study 8835-062 from 31 December 2023 to 31 October 2024, following approval of the post-authorisation measure procedure EMEA/H/C/004313-5/MEA/002.5

15.2.6. [Fenfluramine - FINTEPLA \(CAP\) - EMEA/H/C/003933/II/0017, Orphan](#)

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 2.10 in order to implement a targeted follow-up questionnaire (FUQ) to further improve the collection of follow-up information on cases of vascular heart disease (VHD) and pulmonary arterial hypertension (PAH) suggested by PRAC following PSUSA/00010907/2021122

15.2.7. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS2535/0053; NEPARVIS (CAP) - EMEA/H/C/004343/WS2535/0051

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of a consolidated RMP for Entresto and its duplicate marketing authorisation Neparvis following approval of: RMP version 4.2 (EMEA/H/C/004062/X/0044/G for Entresto and EMEA/H/C/004343/X/0042/G for Neparvis); RMP version 5.0 (EMEA/H/C/004062/WS2434/G for Entresto and EMEA/H/C/004343/WS2434/G for Neparvis) and RMP version 6.0 (EMEA/H/C/004062/WS2465 for Entresto and EMEA/H/C/004343/WS2465 for Neparvis)

15.2.8. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/WS2541/0040; RYBELSUS (CAP) - EMEA/H/C/004953/WS2541/0035

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Mari Thorn

Scope: Submission of an updated RMP version 8.1 following assessment of the same for the reference product Wegovy (EMEA/H/C/005422/II/0009 approved on 28 April 2023). The Semaglutide RMP which is shared with all three Semaglutide products (Rybelsus, Ozempic, Wegovy) was updated due to an extension of the Wegovy label to include an indication in the adolescent population. The RMP's for Rybelsus (oral semaglutide for treatment of Type 2 Diabetes) and Ozempic (sc. semaglutide for treatment for Type 2 Diabetes) have been updated accordingly. Please note that no labelling changes will be made in this procedure because the investigation into efficacy and safety in pediatric population above 10 years of age according to agreed PIPs for Ozempic and Rybelsus is still ongoing

15.2.9. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0064

Applicant: Amgen Europe B.V., ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 11.0 in order to remove the important potential risk of "talimogene laherparepvec-mediated anti-GM-CSF antibody response", based on the accumulated scientific and clinical data

15.2.10. Tixagevimab, cilgavimab - EVUSHELD (CAP) - EMEA/H/C/005788/II/0013

Applicant: AstraZeneca AB

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of an updated RMP version 5 succession 1 to remove the commitment to conduct the PASS D8850R00006: A post-authorisation Observational Study of Women exposed to EVUSHELD During Pregnancy (O-STEREO)

15.2.11. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0054

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 31.1 in order to modify study A3921427 from an interventional to a non-interventional study. In addition, the MAH has taken the opportunity to update other sections of the RMP

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

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

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

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

15.3.2. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/II/0069, Orphan

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information following results from study PTC124-GD-041-DMD, listed as a specific obligation in the Annex II; this is a Phase 3 multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open label extension to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nonsense mutation Duchenne muscular dystrophy (mnDMD) aged 5 years or older. Annex II, and Annex IIB are updated to delete the SOB and to reflect the switch from conditional to full marketing authorisation. The package leaflet is updated accordingly. The RMP version 11.0 has also been submitted. Minor corrections were done to align the product information with the latest QRD templates

15.3.3. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0078

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Update of section 5.1 of the SmPC in order to include the final overall survival (OS) analysis results based on final results from study WO30070 listed as a PAES in the Annex II to fulfil ANX/PAE 003; this is a Phase III, multicenter, randomised, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in

patients with untreated locally advanced or metastatic urothelial carcinoma. The RMP version 27 has also been submitted. In addition, the MAH took the opportunity to update Annex II of the SmPC

15.3.4. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0023, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with indolent systemic mastocytosis (ISM) for avapritinib based on results from the pivotal part of study BLU-285-2203 (PIONEER); this is a 3-part, randomised, double-blind, placebo-controlled, Phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285) in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted

15.3.5. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0037

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include the treatment of paediatric patients (from 2 years of age and older) with moderate to severe atopic dermatitis for OLUMIANT, based on the final results from study I4V-MC-JAIP; this is a Phase III, multicentre, randomised, double blind, placebo controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe atopic dermatitis. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 of the SmPC are updated. The package leaflet has been updated accordingly. Version 17.1 of the RMP has also been submitted

15.3.6. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0107, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include treatment of adult patients with previously untreated CD30+ advanced (including Stage III) Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine and dacarbazine (AVD), for ADCETRIS, based on the second interim analysis of overall survival (OS) data from ECHELON-1 study (C25003); this is a randomised, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical HL. As a consequence, sections 4.1 and 5 of the SmPC are updated

15.3.7. Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/II/0021, Orphan

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a product information, have demonstrated disease progression on or after the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing, Phase 3, randomised, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the product information. As part of the application the MAH is requesting a 1-year extension of the market protection

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

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

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

15.3.9. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/X/0017/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application consisting of: 1) Extension application to: a) Introduce a new pharmaceutical form (coated granules) associated with a new strength (50 mg); b) Introduce a new route of administration (gastroenteral use) for the already authorised 100 mg and 200 mg hard capsules presentations based on final results from studies CO40778 (STARTRK-NG), GO40782 (STARTRK-2) and BO41932 (TAPISTRY). Study CO40778 is a Phase I/II open-label, dose-escalation and expansion study of entrectinib in pediatrics with locally advanced or metastatic solid or primary CNS tumors and/or who have no satisfactory treatment options; Study GO40782 is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumors that harbor an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion), and Study BO41932 is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are tumor mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay, grouped with the following type II variations:

a) to extend the currently approved indication in solid tumours with NTRK gene fusion to patients from birth to 12 years of age (both for the coated granules and already approved hard capsules presentations);

b) to add a new paediatric indication from birth to 18 years of age for patients with solid tumours with a ROS1 gene fusion (both for the coated granules and already approved hard capsules presentations).

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated accordingly. The package leaflet and Labelling are updated in accordance.

c) to add wording regarding the option of suspension in water of the content of the capsules to be used orally or via the e.g. gastric or nasogastric tube (in sections 4.2 and 5.2 of the SmPC).

The RMP (version 5) is updated in accordance. The MAH took the opportunity to introduce minor editorial changes to the product information and to update Annex II of the SmPC

15.3.10. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/II/0011

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Extension of indication to include the treatment of paediatric patients with homozygous familial hypercholesterolaemia (HoFH) aged 5 years and older for EVKEEZA, based on interim results from study R1500-CL-17100, as well as supportive information from an updated interim analysis of study R1500-CL-1719, and an extrapolation analysis (including population PK, population PK/PD, and simulation analyses). R1500-CL-17100 is an ongoing multicentre, three-part, single-arm, open-label study evaluating the efficacy, safety, and tolerability of evinacumab in paediatric patients aged ≥ 5 to 11 years with HoFH. 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 1.1 of the RMP has also been submitted. In addition, the marketing authorisation holder took the opportunity to introduce minor editorial changes to the product information. Furthermore, the product information is brought in line with the latest QRD template version 10.3

15.3.11. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58³²) - EMEA/H/W/002320/II/0016

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Liana Gross-Martirosyan

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

³² 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)

leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted

15.3.12. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0013/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final reports from studies ALN-AS1-003 (Study 003) and ALN-AS1-002 (Study 002) listed as a category 3 studies in the RMP. Study 003 is a phase 3 randomised, double-blind, placebo-controlled multicenter study with an open-label extension to evaluate the efficacy and safety of givosiran in patients with acute hepatic porphyrias, while Study 002 is a multicentre, open-label extension study to evaluate the long-term safety and clinical activity of subcutaneously administered ALN AS1 in patients with acute intermittent porphyria who have completed a previous clinical study with ALN-AS1. The RMP version 2.2 has also been submitted

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

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Amelia Cupelli

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

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

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults for HyQvia, based on final results from studies 161403 and ABV-771-1001; and interim results from study 161505. 161403 and 161505 are interventional Phase III efficacy and safety studies respectively, while ABV-771-1001 is an interventional Phase I safety study. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 14.0 of the RMP has also been submitted

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

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Gabriele Maurer

Scope: Update of sections 4.2, 4.6, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies ITCC-059 (WI203581) and INO-Ped-ALL-1 (WI235086). Study WI203581 is a Phase 1/2, multicenter, European, multi-

cohort, open-label study in pediatric patients (≥ 1 and < 18 years of age) with R/R CD22-positive Acute Lymphoblastic Leukemia (ALL); and study WI235086 is an open-label, multi-center Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive ALL. The package leaflet is updated accordingly. The RMP version 2.0 has also been submitted

15.3.16. [Ivacaftor, tezacaftor, elexacaftor - KAFTRIO \(CAP\) - EMEA/H/C/005269/II/0035, Orphan](#)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

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

15.3.17. [Ivacaftor, tezacaftor, elexacaftor - KAFTRIO \(CAP\) - EMEA/H/C/005269/II/0039, Orphan](#)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update information based on final results from study VX17-445-105 (study 105); this is a phase 3, open-label, extension study evaluating the long-term safety and efficacy of ELX/TEZ/IVA treatment in cystic fibrosis (CF) subjects 12 years of age and older, homozygous, or heterozygous for the F508del-CFTR mutation who participated in study VX17-445-102 (study 102) or study VX17-445-103 (study 103). The RMP version 7.2 has also been submitted

15.3.18. [Ivacaftor, tezacaftor, elexacaftor - KAFTRIO \(CAP\) - EMEA/H/C/005269/X/0033, Orphan](#)

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: Extension application to add a new pharmaceutical form (granules) associated with 2 new strengths (60 mg/40 mg/80 mg and 75 mg/50 mg/100 mg) to support a new indication in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1). The new indication is only applicable to the new granules pharmaceutical form. As a consequence of the line extension the product information for the film coated tablets is also updated to reflect the addition of a new pharmaceutical form. The RMP (version 6.2) has also been submitted

15.3.19. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0045, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the Clinical Study Report (Addendum 2) for study C16019 listed as a Specific Obligation in the Annex II of the product information. This is a phase 3, randomised, double-blind, placebo-controlled study of single-agent oral ixazomib as maintenance therapy following autologous stem cell transplant (ASCT) for patients with newly diagnosed multiple myeloma. In addition, the MAH proposes to remove NINLARO from the list of medicines subject to additional monitoring and to remove the black triangle from the SmPC. 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 and update the list of local representatives in the package leaflet

15.3.20. Lanadelumab - TAKHZYRO (CAP) - EMEA/H/C/004806/X/0034/G, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped application consisting of: 1) Extension application to add a new strength of 150 mg for lanadelumab solution for injection in pre-filled syringe and to extend the indication to include paediatric use (2 to <12 years). The new indication is only applicable to the new 150 mg strength presentations. The RMP (version 3.0) is updated in accordance; 2) a type IB variation (C.I.z) to update section 7 of the package leaflet (PL) for the 300 mg in 2 ml pre-filled syringe (EU/1/18/1340/004-006) in line with the proposed package leaflet for the 150 mg in 1 ml pre-filled syringe (new strength). In addition, the MAH has requested an extension of the Orphan Market Exclusivity from 10 to 12 years

15.3.21. Lenvatinib - LENVIMA (CAP) - EMEA/H/C/003727/II/0050

Applicant: Eisai GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies E7080-G000-207 and E7080-G000-230. Study E7080-G000-207 is a multicenter, open-label, Phase 1/2 study of lenvatinib in children and adolescents with refractory or relapsed solid malignancies and young adults with osteosarcoma; Study E7080-G000-230 is a multicenter, open-label, randomised Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents and young adults with Relapsed or Refractory Osteosarcoma (OLIE). The package leaflet is updated accordingly. The RMP version 15.1 has also been submitted

15.3.22. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/II/0080

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Update of sections 4.2, 4.6, and 4.8 of the SmPC in order to modify administration instructions recommendation regarding the monitoring of pre-prandial blood glucose in pre prandial condition and in case of symptoms and to prevent the risk of lipohypertrophy, delete wording in the pregnancy section and update on number of patients with severe primary IGD deficiency (IGFD) based on the cumulative review of safety database, scientific literature and clinical trials data. The package leaflet is updated accordingly. The RMP version 14.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.23. Methotrexate - NORDIMET (CAP) - EMEA/H/C/003983/II/0027

Applicant: Nordic Group B.V.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include treatment of moderate to severe recalcitrant disabling psoriasis for Nordimet, based on literature. As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The package leaflet is updated in accordance. The RMP (version 6.0) of the RMP has also been submitted

15.3.24. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/X/0132

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension application to introduce a new recombinant Chinese hamster ovary (CHO) host monoclonal cell line (BMSCHO1-nivolumab) and a new manufacturing process of the active substance. The RMP (version 34) is updated in accordance. In addition, the MAH took the opportunity to update the Annex II in the product information. Consequentially, the following manufacturers of the biological active substance have been removed from the dossier (module 3.2.S.2.1 and Annex II of the product information):

- Lotte Biologics USA, LLC (6000 Thompson Road, East Syracuse, New York 13057, USA)
- Lonza Biologics, Inc. (101 International Drive, Portsmouth, New Hampshire 03801, USA)
- Samsung Biologics Co. Ltd. (300, Songdo Bio Way (Daero), Yeonsu-gu, Incheon, 21987, Korea)

15.3.25. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0064

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.8 and 5.1 of the SmPC to update the results of a descriptive analysis of Overall Survival at seven years last subject randomised in study D0818C0001 (SOLO1). This is a Phase III randomised, double blind, placebo controlled, multicentre study in which advanced ovarian cancer patients with BRCA mutations who had responded following first-line platinum-based chemotherapy were randomised 2:1 to receive either Olaparib (300 mg bd, tablet formulation) or placebo. The RMP version 28 has also been submitted. In addition, the MAH took the opportunity to update section D of Annex II

15.3.26. [Onasemnogene abeparvovec - ZOLGENSMA \(CAP\) - EMEA/H/C/004750/II/0040, Orphan](#)

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to add a new warning and precaution capturing the theoretical risk of tumorigenicity as a result of vector integration and to include a new statement indicating random instances of vector integration are possible; based on final results from studies 2220205 and 2220117, and literature. The package leaflet is updated accordingly. The RMP version 3 has also been submitted

15.3.27. [Osimertinib - TAGRISSO \(CAP\) - EMEA/H/C/004124/II/0052](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 5.1 of the SmPC in order to update efficacy information (final OS data) based on final results from study D5164C00001 (ADAURA) listed as a PAES in the Annex II; this is a Phase III, double-blind, randomised, placebo-controlled study, designed to assess the efficacy and safety of osimertinib versus placebo in patients with stage IB-IIIa epidermal growth factor receptor mutation positive (EGFRm) non-small cell lung cancer (NSCLC) who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy. The RMP version 15 has also been submitted. In addition, the MAH took the opportunity to update Annex II section D of the product information and to implement editorial changes to the SmPC

15.3.28. [Patiromer - VELTASSA \(CAP\) - EMEA/H/C/004180/X/0031/G](#)

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kirsti Villikka

Scope: Extension application to introduce a new strength (1 g powder for oral suspension), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of population from 6 to 18 years old for Veltassa based on final results from paediatric study RLY5016-206P (EMERALD); this is a phase 2, open-label, multiple dose study to evaluate the pharmacodynamic effects, safety, and tolerability of patiromer for oral suspension in children and adolescents 2 to less than 18 years of age with chronic kidney disease and hyperkalaemia. As a consequence, sections 1, 2, 4.1, 4.2, 4.8, 4.9, 5.1 and 6.5 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes

15.3.29. [Pembrolizumab - KEYTRUDA \(CAP\) - EMEA/H/C/003820/II/0121](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with stage IB (T2a \geq 4 cm), II or IIIA non-small cell lung carcinoma

(NSCLC) who have undergone complete resection, based on study KEYNOTE-091: an ongoing phase 3, randomised, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the package leaflet is updated in accordance. An updated RMP version 39.1 was also submitted

15.3.30. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0138

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include KEYTRUDA in combination with gemcitabine-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults, based on final results from study KEYNOTE-966; this is a Phase 3 randomised, double-blind study of Pembrolizumab plus Gemcitabine/Cisplatin versus Placebo plus Gemcitabine/Cisplatin as first-line therapy in participants with advanced and/or unresectable biliary tract carcinoma. As a consequence, sections 4.1, 4.4 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 43.1 of the RMP has also been submitted

15.3.31. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/II/0050

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC in order to address the safety of remdesivir and its metabolites in patients with hepatic impairment and to update information on hepatic and coagulation laboratory abnormalities based on final results from study GS US 540 9014 (listed as category 3 study in the RMP): a phase 1 open-label, adaptive, single-dose study to evaluate the pharmacokinetics of remdesivir and its metabolite(s) in subjects with normal hepatic function and hepatic impairment, and on safety data from post-marketing and clinical trials experience. The package leaflet is updated accordingly. The RMP version 5.4 has also been submitted. In addition, the MAH took the opportunity submit Minor Linguistic Amendments (MLA) for Veklury

15.3.32. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0036

Applicant: Zr Pharma& GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include maintenance treatment of adult patients with advanced (FIGO Stages III and IV) epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC) who are in response (complete or partial) to first-line platinum-based chemotherapy for RUBRACA, based on interim results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). 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 6.3 of the

RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection

15.3.33. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0035

Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (350 mg/ml oral solution). The RMP (version 0.1) is updated in accordance

15.3.34. Tepotinib - TEPMETKO (CAP) - EMEA/H/C/005524/II/0009

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update safety and efficacy information based on results from study VISION (MS200095-0022); this is a Phase II, multicenter, open-label, single-arm study to evaluate the efficacy and safety/tolerability of the recommended dose of tepotinib in participants with advanced NSCLC of all histology types who tested positive for METex14 skipping alterations by next-generation sequencing in tissue (RNA-based) or plasma (circulating tumor DNA based). The RMP version 2.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.35. Vosoritide - VOXZOGO (CAP) - EMEA/H/C/005475/II/0006, Orphan

Applicant: BioMarin International Limited

PRAC Rapporteur: Zane Neikena

Scope: Extension of indication to include treatment of children less than 2 years of age for Voxzogo, based on the final results from the category 1 study BMN 111-206 and interim results from its open-label extension study 111-208. 111-206 is a phase 2 randomised, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy of BMN 111 in infants and young children with achondroplasia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and package leaflet are updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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. Adalimumab - AMGEVITA (CAP); AMSPARITY (CAP); HEFIYA (CAP); HUKYNDRA (CAP); HULIO (CAP); HUMIRA (CAP); HYRIMOZ (CAP); IDACIO (CAP); IMRALDI (CAP); LIBMYRIS (CAP); YUFLYMA (CAP) - PSUSA/00010783/202212

Applicant: Amgen Europe B.V. (AMGEVITA), Pfizer Europe MA EEIG (Amsparity), STADA Arzneimittel AG (Hukyndra, Libmyris), Viatris Limited (Hulio), AbbVie Deutschland GmbH & Co. KG (Humira), Sandoz GmbH (Hefiya, Hyrimoz), Fresenius Kabi Deutschland GmbH (Idacio), Samsung Bioepis NL B.V. (Imraldi), Celltrion Healthcare Hungary Kft. (Yuflyma)

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.2. Anifrolumab - SAPHNELO (CAP) - PSUSA/00010980/202301

Applicant: AstraZeneca AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202301

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.4. Avalglucosidase alfa - NEXVIADYME (CAP) - PSUSA/00011002/202302

Applicant: Sanofi B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.5. Avapritinib - AYVAKYT (CAP) - PSUSA/00010878/202301

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.6. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202302

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. [Birch bark extract³³ - FILSUEZ \(CAP\) - PSUSA/00010446/202301](#)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.8. [Botulinum toxin type A³⁴ - NUCEIVA \(CAP\) - PSUSA/00010796/202301](#)

Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. [Bulevirtide - HEPCLUDEX \(CAP\) - PSUSA/00010873/202301](#)

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. [Casirivimab, imdevimab \(Ronapreve\) - RONAPREVE \(CAP\) - PSUSA/00010963/202301](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.11. [Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID \(CAP\) - PSUSA/00010028/202212](#)

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.12. [Dapivirine - DAPIVIRINE VAGINAL RING 25 MG \(Art 58³⁵\) - EMEA/H/W/002168/PSUV/0021](#)

Applicant: International Partnership for Microbicides Belgium AISBL

PRAC Rapporteur: Jan Neuhauser; PRAC Co-rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUR procedure

³³ Centrally authorised product(s) only

³⁴ Centrally authorised product(s) only

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)

16.1.13. Daridorexant - QUVIVIQ (CAP) - PSUSA/00010993/202301

Applicant: Idorsia Pharmaceuticals Deutschland GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.14. Dasabuvir - EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010773/202301

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.15. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202301

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.16. Eptacog beta (activated) - CEVENFACTA (CAP) - PSUSA/00011006/202301

Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.17. Eptifibatide - INTEGRILIN (CAP) - PSUSA/00001246/202301

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.18. Faricimab - VABYSMO (CAP) - PSUSA/00011016/202301

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.19. Finerenone - KERENDIA (CAP) - PSUSA/00010978/202301

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.20. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202302

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.21. Glucagon³⁶ - BAQSIMI (CAP); OGLUO (CAP) - PSUSA/00010826/202301

Applicant: Eli Lilly Nederland B.V. (BAQSIMI), Tetris Pharma B.V. (Ogluo)

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.22. Glucarpidase - VORAXAZE (CAP) - PSUSA/00010968/202301

Applicant: SERB S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.23. Imipenem, cilastatin, relebactam - RECARBRIO (CAP) - PSUSA/00010830/202301

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.24. Inclisiran - LEQVIO (CAP) - PSUSA/00010904/202212

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.25. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/00010990/202302

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.26. Lixisenatide - LYXUMIA (CAP) - PSUSA/00010017/202301

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

³⁶ Centrally authorised product(s) only

16.1.27. Lonoctocog alfa - AFSTYLA (CAP) - PSUSA/00010559/202301

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.1.28. Melphalan flufenamide - PEPAXTI (CAP) - PSUSA/00011013/202302

Applicant: Oncopeptides AB

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.29. Metreleptin - MYALEPTA (CAP) - PSUSA/00010700/202301

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.30. Odevixibat - BYLVAY (CAP) - PSUSA/00010949/202301

Applicant: Albireo

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.31. Omalizumab - XOLAIR (CAP) - PSUSA/00002214/202212

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.32. Osilodrostat - ISTURISA (CAP) - PSUSA/00010820/202301

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.33. Plerixafor - MOZOBIL (CAP) - PSUSA/00002451/202212

Applicant: Sanofi B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.34. [Pneumococcal polysaccharide conjugate vaccine \(15 valent, adsorbed\) - VAXNEUVANCE \(CAP\) - PSUSA/00010975/202301](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.35. [Pneumococcal polysaccharide conjugate vaccine \(10-valent, adsorbed\) - SYNFLORIX \(CAP\) - PSUSA/00009262/202212](#)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.36. [Pneumococcal polysaccharide conjugate vaccine \(13-valent, adsorbed\) - PREVENAR 13 \(CAP\) - PSUSA/00009263/202301 \(with RMP\)](#)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.37. [Quadrivalent influenza vaccine \(recombinant, prepared in cell culture\) - SUPEMTEK \(CAP\) - PSUSA/00010886/202301](#)

Applicant: Sanofi Pasteur

PRAC Rapporteur: Nathalie Gault

Scope: Evaluation of a PSUSA procedure

16.1.38. [Ravulizumab - ULTOMIRIS \(CAP\) - PSUSA/00010787/202212](#)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.39. [Regdanvimab - REGKIRONA \(CAP\) - PSUSA/00010964/202302](#)

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Valentina Di Giovanni

Scope: Evaluation of a PSUSA procedure

16.1.40. [Remimazolam - BYFAVO \(CAP\) - PSUSA/00010924/202301](#)

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.41. [Risdiplam - EVRYSDI \(CAP\) - PSUSA/00010925/202302](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.42. [Romosozumab - EVENITY \(CAP\) - PSUSA/00010824/202301](#)

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.43. [Rufinamide - INOVELON \(CAP\) - PSUSA/00002671/202301](#)

Applicant: Eisai GmbH

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.44. [Salmeterol, fluticasone propionate³⁷ - BROPAIR SPIROMAX \(CAP\); SEFFALAIR SPIROMAX \(CAP\) - PSUSA/00010928/202301](#)

Applicant: Teva B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.45. [Sarilumab - KEVZARA \(CAP\) - PSUSA/00010609/202301](#)

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Monica Martinez Redondo

Scope: Evaluation of a PSUSA procedure

16.1.46. [Smallpox vaccine and monkeypox \(live, modified vaccinia virus Ankara\) - IMVANEX \(CAP\) - PSUSA/00010119/202301](#)

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.47. [Sutimlimab - ENJAYMO \(CAP\) - PSUSA/00011023/202302](#)

Applicant: Sanofi B.V.

³⁷ Centrally authorised product(s) only

PRAC Rapporteur: Jan Neuhauser
Scope: Evaluation of a PSUSA procedure

16.1.48. Tafasitamab - MINJUVI (CAP) - PSUSA/00010951/202301

Applicant: Incyte Biosciences Distribution B.V.
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.49. Tecovirimat - TECOVIRIMAT SIGA (CAP) - PSUSA/00010971/202301

Applicant: SIGA Technologies Netherlands B.V.
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.50. Tipranavir - APTIVUS (CAP) - PSUSA/00002973/202212 (with RMP)

Applicant: Boehringer Ingelheim International GmbH
PRAC Rapporteur: Nathalie Gault
Scope: Evaluation of a PSUSA procedure

16.1.51. Ustekinumab - STELARA (CAP) - PSUSA/00003085/202212

Applicant: Janssen-Cilag International N.V.
PRAC Rapporteur: Rhea Fitzgerald
Scope: Evaluation of a PSUSA procedure

16.1.52. Vericiguat - VERQUVO (CAP) - PSUSA/00010950/202301

Applicant: Bayer AG
PRAC Rapporteur: Kimmo Jaakkola
Scope: Evaluation of a PSUSA procedure

16.1.53. Voclosporin - LUPKYNIS (CAP) - PSUSA/00011020/202301

Applicant: Otsuka Pharmaceutical Netherlands B.V.
PRAC Rapporteur: Adam Przybylkowski
Scope: Evaluation of a PSUSA procedure

16.1.54. Vonicog alfa - VEYVONDI (CAP) - PSUSA/00010714/202212

Applicant: Baxalta Innovations GmbH
PRAC Rapporteur: Mari Thorn

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. ¹³C-urea, ¹⁴C-urea - HELICOBACTER TEST INFAI (CAP); PYLOBACTELL (CAP); NAP - PSUSA/00000006/202301

Applicant: INFAI GmbH (Helicobacter Test INFAI), Richen Europe S.r.l. (Pylobactell), various

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.2.2. Lenalidomide - LENALIDOMIDE ACCORD (CAP); LENALIDOMIDE KRKA (CAP); LENALIDOMIDE KRKA D.D. (SRD) (CAP); LENALIDOMIDE KRKA D.D. NOVO MESTO (CAP); LENALIDOMIDE MYLAN (CAP); REVLIMID (CAP); NAP - PSUSA/00001838/202212

Applicant: Accord Healthcare S.L.U. (Lenalidomide Accord), Krka d.d. Novo mesto (Lenalidomide Krka), KRKA, d.d., Novo mesto (Lenalidomide Krka d.d. (SRD), Lenalidomide Krka d.d. Novo mesto), Mylan Ireland Limited (Lenalidomide Mylan), Bristol-Myers Squibb Pharma EEIG (Revlimid), various

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.2.3. Oxybutynin - KENTERA (CAP); NAP - PSUSA/00002253/202207

Applicant(s): Teva B.V. (Kentera), various

PRAC Rapporteur: Jo Robays

Scope: Evaluation of a PSUSA procedure

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

16.3.1. 5-fluorouracil³⁸ (NAP) - PSUSA/00010000/202301

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.2. Allergen for therapy: Dactylis Glomerata L., Phleum Pratense L., Anthoxanthum Odoratum L., Lolium Perenne L., Poa Pratensis L.³⁹ (NAP) - PSUSA/00010465/202212

Applicant(s): various

³⁸ For topical formulation(s) only

³⁹ Sublingual tablet only

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.3. Aldesleukin (NAP) - PSUSA/00000076/202212

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.4. Alitretinoin⁴⁰ (NAP) - PSUSA/00010710/202301

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.5. Amisulpride (NAP) - PSUSA/00000167/202301

Applicant(s): various

PRAC Lead: Eamon O'Murchu

Scope: Evaluation of a PSUSA procedure

16.3.6. Atracurium (NAP) - PSUSA/00000267/202212

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.7. Calcium chloride dihydrate, magnesium chloride hexahydrate, malic acid, sodium acetate trihydrate, sodium chloride, potassium chloride/calcium chloride dihydrate, sodium chloride, sodium lactate, potassium chloride/calcium chloride, sodium chloride, potassium chloride (NAP) - PSUSA/00010622/202301

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

16.3.8. Cefprozil (NAP) - PSUSA/00000605/202212

Applicant(s): various

PRAC Lead: Polona Golmajer

Scope: Evaluation of a PSUSA procedure

⁴⁰ Oral use only

16.3.9. Cilostazol (NAP) - PSUSA/00010209/202301

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.10. Cimicifuga racemosa (L.) Nutt., rhizoma (NAP) - PSUSA/00000755/202301

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.11. Cisplatin (NAP) - PSUSA/00000778/202212

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.3.12. Codeine camphosulphonate, sodium benzoate, codeine camphosulphonate, sulfogaiacol, grindelia soft extract (NAP) - PSUSA/00010542/202212

Applicant(s): various

PRAC Lead: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.3.13. Enalapril, nitrendipine (NAP) - PSUSA/00001213/202301

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.14. Felodipine (NAP) - PSUSA/00001356/202212

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.15. Furosemide (NAP) - PSUSA/00001491/202301

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.16. *Haemophilus influenzae*, *klebsiella ozaenae*, *klebsiella pneumoniae*, *moraxella catarrhalis*, *staphylococcus aureus*, *streptococcus pneumoniae*, *streptococcus pyogenes*, *streptococcus viridans* vaccine (NAP) - PSUSA/00001582/202212

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.17. *Hypericum perforatum* L., herba (NAP) - PSUSA/00001701/202301

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.18. *Ibutilide* (NAP) - PSUSA/00001713/202212

Applicant(s): various

PRAC Lead: Georgia Gkegka

Scope: Evaluation of a PSUSA procedure

16.3.19. *Levobupivacaine* (NAP) - PSUSA/00001848/202212

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.20. *Sertindole* (NAP) - PSUSA/00002695/202301

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

16.3.21. *Tetanus vaccines* (NAP) - PSUSA/00002910/202301

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. *Dolutegravir* - TIVICAY (CAP) - EMEA/H/C/002753/LEG 015.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 015.2 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per the request for supplementary information (RSI) adopted in February 2023

16.4.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/LEG 010.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to LEG 010.2 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per the request for supplementary information (RSI) adopted in February 2023

16.4.3. Dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/LEG 005.3

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: David Olsen

Scope: MAH's response to LEG 005.2 [Submission of all available data/results for study RESPOND (International Cohort Consortium of Infectious Disease): a prospective, multi-cohort collaboration study of people living with human immunodeficiency virus (HIV) across Europe and Australia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010075/202101) adopted in September 2021] as per the request for supplementary information (RSI) adopted in February 2023

16.4.4. Tisagenlecleucel - KYMRIA (CAP) - EMEA/H/C/004090/LEG 021

Applicant: Novartis Europharm Limited, ATMP

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of further data on cases of secondary malignancies, as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010702/202208) adopted in March 2023

16.4.5. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/LEG 063

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of cumulative reviews of cases of psychiatric disorders including depression and related disorders, ulcerative keratitis, and pyoderma gangrenosum from clinical trials data, post-marketing studies, literature and spontaneous reports as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002980/202204) adopted in December 2022

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0063

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an update of sections 4.3, 4.4 and 4.5 of the SmPC to update and streamline the relevant wording on opioids as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010366/202209) adopted in April 2023. The package leaflet is updated accordingly. The RMP version 12.9 has also been submitted

16.6. Expedited summary safety reviews⁴¹

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)⁴²

17.1.1. Fosdenopterin – NULIBRY (CAP) - EMEA/H/C/PSP/S/0103.1

Applicant: Zydus France S.A.S.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/0103 [PASS to characterise and assess the long-term safety and efficacy of NULIBRY prescribed in routine practice for patients with MoCD Type A] as per the request to supplementary information (RSI) adopted in April 2023

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴³

17.2.1. Birch bark extract - FILSUEVZ (CAP) - EMEA/H/C/005035/MEA 001.1

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Zane Neikena

Scope: MAH's response to MEA 001 [Submission of a protocol for Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in epidermolysis bullosa (EB) (FOStER-EB) [(AEB-21)] (listed as category 3 study in the RMP) to evaluate the long-term

⁴¹ 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

⁴² In accordance with Article 107n of Directive 2001/83/EC

⁴³ 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

safety of Filisuvez amongst patients treated for EB in relation to the incidence, severity and relatedness of skin malignancies (including squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma (MM)), and use in patients with different skin types regarding ethnic origin] as per request for supplementary information (RSI) adopted in March 2023

17.2.2. Brodalumab - KYNTHEUM (CAP) - EMEA/H/C/003959/MEA 002.7

Applicant: LEO Pharma A/S

PRAC Rapporteur: Monica Martinez Redondo

Scope: Revised protocol (version 6.0) for PASS KYNTHEUM-1345: The BRodalumab Assessment of Hazards: A Multinational Safety (BRAHMS) study in electronic healthcare databases – an observational PASS of suicidal behaviour, serious infections, major adverse cardiac events (MACE) and malignancy in psoriasis patients treated with brodalumab (Kyntheum)

17.2.3. Ciltacabtagene autoleucl - CARVYKTI (CAP) - EMEA/H/C/005095/MEA 007.2

Applicant: Janssen-Cilag International NV, ATMP

PRAC Rapporteur: Jo Robays

Scope: MAH's response to MEA 007.1 [Submission of a revised protocol for study PCSONCA0014: a survey to evaluate the effectiveness of the ciltacabtagene autoleucl HCP Educational Program and the Product Handling Training] as per the request for supplementary information (RSI) adopted in April 2023

17.2.4. Coronavirus (COVID-19) vaccine (recombinant, adjuvanted) - NUVAXOVID (CAP) - EMEA/H/C/005808/MEA 006.2

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: Updated protocol version 3.0 for study 2019nCoV-404: US PASS to evaluate the pooled of risk of selected adverse events of special interest (AESI) within specified time periods after vaccination with Nuvaxovid using a claim and/or electronic healthcare record (her) database

17.2.5. Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study IM011194: long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194) to evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting

17.2.6. Fexinidazole - FEXINIDAZOLE WINTHROP (Art 58⁴⁴) - EMEA/H/W/002320/MEA 002.3

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.2 [Protocol for study FEXINC09395: a prospective observational study of the safety of fexinidazole for human African trypanosomiasis] as per the request for supplementary information (RSI) adopted in April 2023

17.2.7. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 016.3

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 016.2 [Revised protocol for study GLPG0634-CL-413: a non-interventional, PASS of filgotinib in patients with moderately to severely active ulcerative colitis (a European multi registry-based study) as per the request for supplementary information (RSI) adopted in March 2023

17.2.8. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 017

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study GLPG0634-CL-417: non-interventional, post-authorisation, cohort, safety study evaluating the effectiveness of the additional risk minimization measures for filgotinib (Jyseleca) use in patients with moderately to severely active ulcerative colitis within multiple European registries

17.2.9. Maribavir - LIVTENCITY (CAP) - EMEA/H/C/005787/MEA 005

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol version 1.0 for study TAK-620-4007: Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid endstage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis

17.2.10. Niraparib, abiraterone acetate - AKEEGA (CAP) - EMEA/H/C/005932/MEA 001

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Feasibility assessment for a PASS to characterize the risk of second primary malignancies (SPM) including MDS/AML among metastatic prostate cancer patients exposed

⁴⁴ 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)

to AKEEGA

17.2.11. Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481/MEA 001

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Protocol for study CA224122 to evaluate Grades 3-4 AEs (which includes irARs) experienced by paediatric patients ≥ 12 to < 18 years of age, along with their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development)

17.2.12. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.5

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol amendment for study 165-501: a multicentre, prospective global observational study to evaluate the long term safety of subcutaneous injections of pegvaliase in patients with phenylketonuria

17.2.13. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 001.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Updated protocol and second annual interim report for study BHV3000-402: a Prospective, Registry-based, Observational Study to Assess Maternal, Fetal, and Infant Outcomes following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR)

17.2.14. Rimegepant - VYDURA (CAP) - EMEA/H/C/005725/MEA 002.2

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Updated protocol and second annual interim report for study BHV3000-402: a Prospective, Registry-based, Observational Study to Assess Maternal, Fetal, and Infant Outcomes following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR)

17.2.15. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.3

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Julia Pallos

Scope: Submission of a revised protocol (version no. 4.0) for study JZP865-401: a PASS to evaluate the long-term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol

17.2.16. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 018.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 018.2 and revised protocol for study A3921407: a post-authorisation active safety surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry

17.2.17. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 019.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 019.2 and revised protocol for study 3921408: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the Swedish juvenile idiopathic arthritis (JIA) clinical registry

17.2.18. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 020.3

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 020.2 and revised protocol for study A3921409: a PASS surveillance programme among patients treated with tofacitinib for polyarticular course juvenile idiopathic arthritis and juvenile psoriatic arthritis (PsA) within the UK juvenile idiopathic arthritis (JIA) biologics register

17.2.19. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 025.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 025 and revised protocol for study No921403 [(listed as category 3 study in the RMP): a PASS of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative Healthcare Database in France: a descriptive drug utilisation study using real-world data collected from routine clinical care in France. The overall goal is to determine if there is evidence that prescribers in France are compliant with the recommendations and limitations for use described in the tofacitinib additional risk minimisation measures (aRMM) materials] as per the request for supplementary information (RSI) adopted in March 2023

17.2.20. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.7

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol amendment for study C4591021 (previously known as vAcCine Covid-19 monitoring readinESS/Vaccine monitoring Collaboration for Europe (ACCESS/VAC4EU)): an assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 messenger ribonucleic acid (mRNA) vaccine estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty (tozinameran) vaccination

17.2.21. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 062.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a protocol for study C4591052: a PASS of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccines in Europe Primary Objective: To determine whether there is an increased risk of pre-specified AESIs following the administration of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine compared with not receiving any COVID-19 bivalent vaccine, in individuals who received a complete primary series of any COVID-19 monovalent vaccine

17.2.22. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 064.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Protocol for a non-interventional post-approval safety study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the United States to ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general US populations (category 3 study in the RMP v9.1 submitted within procedure X-176 and II-177-G)

17.2.23. Vutrisiran - AMVUTTRA (CAP) - EMEA/H/C/005852/MEA 002.1

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002 [protocol amendment for study ALN-TTR02-013, ConTTRIBUTE Study: global, prospective, observational, multicentre long-term study. This is a prospective, observational study that will provide a robust assessment of the long-term safety of Amvuttra in real-world clinical practice along with a comparator group being enrolled in ConTTRIBUTE who follow local standard of care. ConTTRIBUTE aims to document the natural history, clinical characteristics, and management of ATTR amyloidosis as part of routine clinical care. The study cohort will include patients with hATTR amyloidosis under care at the participating study site, as no exclusion criteria are intended with this observational cohort. Patients with hepatic impairment will be observed as part of the cohort. The study will also include data collection on the clinical consequences of vitamin A deficiency, including delayed symptoms, and pregnancy exposure and pregnancy and infant outcomes] as per the request for supplementary information (RSI) adopted in March 2023

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

17.3.1. Chlormadinone acetate, ethinyl estradiol (NAP) - EMEA/H/N/PSR/J/0042

Applicant: GEDEON RICHTER Plc

PRAC Rapporteur: Martin Huber

Scope: Final study report for: risk of venous thromboembolism – The role of oral contraceptives – a case control study comparing levonorgestrel and chlormadinone acetate to compare the VTE risk of combined oral contraceptives (COCs) containing CMA 2mg / ethinylestradiol (EE) 30 µg, compared to COCs containing levonorgestrel (LNG) 0.15mg, both combined with 30 µg ethinylestradiol (EE)

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

17.4.1. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0031

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report from study ARCANGELO (itAlian pRospective study on CANGrELOr), listed as a category 3 study in the RMP. This is a multicentre observational, prospective cohort study including patients with acute coronary syndromes undergoing percutaneous coronary intervention who receive cangrelor i.v. transitioning to either clopidogrel, prasugrel or ticagrelor per os. The primary objective is to assess the safety of cangrelor in a real-world setting, when administered in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI). The safety of cangrelor is based on the incidence of any haemorrhage at 30 days post-PCI. The RMP version 5.1 has also been submitted

17.4.2. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/II/0032

Applicant: Almirall S.A

PRAC Rapporteur: Mari Thorn

Scope: Submission of the final report from study M-41008-44 listed as a category 3 study in the RMP. This is a non-interventional PASS titled 'A retrospective chart review to assess the effectiveness of the Skilarence risk minimisation activities in daily practice'. The RMP version 2.1 has also been submitted

17.4.3. Fenofibrate, pravastatin sodium - PRAVAFENIX (CAP) - EMEA/H/C/001243/II/0034

Applicant: Laboratoires SMB s.a.

PRAC Rapporteur: Nathalie Gault

Scope: Submission of the final report from study POSE: Pravafenix Observational Study in Europe (EUPAS 13661), listed as a category 3 study in the RMP (MEA/007.10). This is an

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

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

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

17.4.4. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA 004.14

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Annual report for the passive enhanced safety surveillance (ESS) D2560C00008: a post-marketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age for the 2021-2022 influenza season. The ESS should be repeated during the vaccination campaign for the flu season 2022-2023. After that, safety surveillance will continue passively and safety data will be discussed through PSURs. The RMP will be updated accordingly

17.4.5. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0070

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 105MS401. The objective of this study was to determine the incidence of serious adverse events (SAEs) in patients with relapsing forms of MS in routine clinical practice and to assess the overall long-term clinical effectiveness of peginterferon beta-1a in patients with relapsing forms of MS in routine clinical practice

17.4.6. Radium (Ra²²³) - XOFIGO (CAP) - EMEA/H/C/002653/II/0052

Applicant: Bayer AG

PRAC Rapporteur: Rugile Pilviniene

Scope: Submission of the final report from study 20702 listed as a category 3 study in the RMP. This is a non-interventional drug utilisation study to investigate the risk of off-label use

17.4.7. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0052

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study A3921334 listed as a category 3 study in the RMP. This is a Non-Interventional PASS to evaluate the effectiveness of additional risk minimisation measures materials for tofacitinib in Europe via a survey of healthcare professionals

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

17.5.1. Afibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 022

Applicant: Bayer AG

PRAC Rapporteur: Nathalie Gault

Scope: Two-year interim study report for FIREFLEYE NEXT Study # 20275: An extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in Study 20090

17.5.2. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - EMEA/H/C/004257/MEA 002.4

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Second progress report for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

17.5.3. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - RIARIFY (CAP) - EMEA/H/C/004836/MEA 002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: First and second progress reports for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

17.5.4. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRYDONIS (CAP) - EMEA/H/C/004702/MEA 002

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: First and second progress reports for study CLI-05993BA1-05 (TRIBE): a multinational database cohort study to assess adverse cardiovascular and cerebrovascular outcomes in patients with chronic obstructive pulmonary disease initiating a fixed triple therapy containing beclometasone dipropionate, formoterol fumarate and glycopyrronium administered via dry powder inhaler (DPI) compared to pressurized metered dose inhaler (pMDI)

17.5.5. [Coronavirus \(COVID-19\) vaccine \(recombinant, adjuvanted\) - NUVAXOVID \(CAP\) - EMEA/H/C/005808/MEA 005.1](#)

Applicant: Novavax CZ, a.s.

PRAC Rapporteur: Gabriele Maurer

Scope: First interim report for study 2019nCoV-405: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER. A registry-based observational cohort safety surveillance study to characterise the population of pregnant women who are vaccinated with Nuvaxovid, estimate the frequency of selected adverse pregnancy outcomes in women and selected adverse foetal/neonatal/infant outcomes at birth and up to the first 12 months of life of infants from pregnancies in women who received Nuvaxovid during pregnancy

17.5.6. [Fenfluramine - FINTEPLA \(CAP\) - EMEA/H/C/003933/MEA 006.3](#)

Applicant: UCB Pharma SA

PRAC Rapporteur: Martin Huber

Scope: Interim report for study EP0220 (old ZX008-2104): A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome (interim analysis) (EUPAS48741) ; Cross-sectional, multicountry, noninterventional survey conducted through an anonymous web questionnaire among physicians who prescribe fenfluramine in European countries

17.5.7. [Fentanyl - INSTANYL \(CAP\) - EMEA/H/C/000959/MEA 029.4](#)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 029.3 [Updated protocol for study Instanyl-5002 (listed as a category 3 study in the RMP): a non-interventional study to assess the effectiveness of updated educational materials on prescribers' knowledge and behaviour with respect to risks associated with Instanyl (fentanyl) off-label use together with an interim report and the statistical analysis plan (SAP)] as per request for supplementary information (RSI) adopted in March 2023 together with an interim report for study Instanyl-5002

17.5.8. [Fingolimod - GILENYA \(CAP\) - EMEA/H/C/002202/MEA 012.12](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Twelfth annual interim report for study D2404 of the Pregnancy Intensive Monitoring program (PRIM)

17.5.9. [Fingolimod - GILENYA \(CAP\) - EMEA/H/C/002202/MEA 038.6](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: MAH's response to MEA 038.5 [Third interim report for study CFTY720D2311: a two-year, double-blind, randomised, multicentre, active-controlled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β -1a intramuscular (IM) once weekly in paediatric patients with multiple sclerosis with five-year fingolimod extension phase] as per the request for supplementary information (RSI) adopted in March 2023

17.5.10. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Jo Robays

Scope: Third annual report for study ACE-536-LTFU-001: a study to evaluate the long-term safety, including thromboembolic events (TEEs) and progression to acute myeloid leukaemia (AML) and/or other malignancies/pre malignancies of luspatercept in patients who have participated in company-sponsored luspatercept clinical trials

17.5.11. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.12

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Progress report for study A-LUT-T-E02-402 (SALUS): an international, non-interventional, post-authorisation long-term safety study of Lutathera (lutetium (^{177}Lu) oxodotreotide) in patients with unresectable or metastatic, well-differentiated, somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumours

17.5.12. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.14

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Final progress report for study D3820R00009 [Naloxegol Health Outcomes PASS – An observational PASS of MOVENTIG (Naloxegol) Among Patients Aged 18 Years and Older Diagnosed with Non- Cancer Pain and Cancer Pain and Treated with Opioids Chronically in Selected European Populations.]

17.5.13. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.5

Applicant: Bayer AG

PRAC Rapporteur: Gabriele Maurer

Scope: Annual report for study 15689: evaluation of AEs of special interest in the PedNet registry (European Paediatric Network for Haemophilia Management) (Epidemiological Study)

17.5.14. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.6

Applicant: Bayer AG

PRAC Rapporteur: Gabriele Maurer

Scope: MAH's response to MEA 004.5 [Thirteenth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry] as per the request for supplementary information (RSI) adopted in April 2023

17.5.15. Ponesimod - PONVORY (CAP) - EMEA/H/C/005163/MEA 001.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: First annual progress report for study POEM: PASS: Ponesimod Pregnancy Outcomes Program Utilizing Enhanced Pharmacovigilance Monitoring

17.5.16. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/MEA 002.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Second annual interim report for study CBAF312A2411 (listed as category 3 study in the RMP): evaluation of pregnancy and infant outcomes in Mayzent patients using pregnancy outcomes intensive monitoring (PRIM)

17.5.17. Sutimlimab - ENJAYMO (CAP) - EMEA/H/C/005776/MEA 003

Applicant: Sanofi B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Annual interim report for study OBS16454: Cold Agglutinin Disease Real World Evidence Registry (CADENCE)

17.5.18. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.7

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 003.6 [Third annual progress report for study M14745-40 (Tildrakizumab PASS in European Psoriasis Registry): To collect long-term safety data in particular relating to event of special interest (important potential risks and pregnancy related outcomes) for tildrakizumab (Malignancies, MACEs, Serious infections, SIBH, Hypersensitivity, IBD, Safety in pregnant and lactating women). To further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical care] as per the request for supplementary information (RSI) adopted in March 2023

17.6. Others

17.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 009.3

Applicant: Sanofi Belgium

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: MAH's responses to ANX 009.2 [The provision of answers to questions about the feasibility report of the noninterventional PASS to investigate the risk of mortality in multiple sclerosis (MS) patients treated with alemtuzumab (Lemtrada) relative to comparable MS patients using other disease modifying treatments (DMTs)] as per request for supplementary information (RSI) adopted in May 2023

17.6.2. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 018

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Feasibility assessment for the filgotinib drug utilization studies in rheumatoid arthritis (GLPG0634-CL-408) and ulcerative colitis (GLPG0634-CL-417) within European registries

17.6.3. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 009.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Justification for early termination of study C4591011: Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System (Study C4591011)

17.6.4. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 047.3

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 047.2 [Initial statistical analysis plan (SAP) for study C4591038 (listed as a category 3 study in the RMP): a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech coronavirus disease 2019 (COVID-19) vaccine to investigate natural history of post-vaccination myocarditis and pericarditis] as per the request for supplementary information (RSI) adopted in March 2023

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. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/005449/S/0010 (without RMP)

Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Mari Thorn

Scope: Annual reassessment of the marketing authorisation

18.1.2. Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/S/0004 (with RMP)

Applicant: SIGA Technologies Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0071 (without RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.2. Loncastuximab tesirine - ZYNLONTA (CAP) - EMEA/H/C/005685/R/0009 (without RMP)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

18.2.3. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0042 (without RMP)

Applicant: Advanz Pharma Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.4. Sotorasib - LUMYKRAS (CAP) - EMEA/H/C/005522/R/0012 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Conditional renewal of the marketing authorisation

18.2.5. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/R/0035 (without RMP)

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Adalimumab - IDACIO (CAP) - EMEA/H/C/004475/R/0022 (without RMP)

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.2. Bevacizumab - ZIRABEV (CAP) - EMEA/H/C/004697/R/0029 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: 5-year renewal of the marketing authorisation

18.3.3. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/R/0044 (without RMP)

Applicant: TEVA GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.4. Lusutrombopag - MULPLEO (CAP) - EMEA/H/C/004720/R/0018 (without RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.5. Macimorelin - GHRYVELIN (CAP) - EMEA/H/C/004660/R/0020 (without RMP)

Applicant: Consilient Health Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.6. Miglustat - MIGLUSTAT DIPHARMA (CAP) - EMEA/H/C/004904/R/0019 (without RMP)

Applicant: DIPHARMA Arzneimittel GmbH

PRAC Rapporteur: Mari Thorn

Scope: 5-year renewal of the marketing authorisation

18.3.7. Naldemedine - RIZMOIC (CAP) - EMEA/H/C/004256/R/0023 (without RMP)

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: 5-year renewal of the marketing authorisation

18.3.8. Pegfilgrastim - PELMEG (CAP) - EMEA/H/C/004700/R/0025 (without RMP)

Applicant: Mundipharma Corporation (Ireland) Limited

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.9. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/R/0039 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.10. Silodosin - SILODOSIN RECORDATI (CAP) - EMEA/H/C/004964/R/0012 (without RMP)

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Valentina Di Giovanni

Scope: 5-year renewal of the marketing authorisation

19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 28 -30 August 2023 meeting.

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	
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	
Željana Margan Koletić	Alternate	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	
Marie Louise Schougaard Christiansen	Member	Denmark	No interests declared	
Maia Uusküla	Member	Estonia	No interests declared	
Kirsti Villikka	Member	Finland	No interests declared	
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 participation in final deliberations	4.1.1. Nivolumab – OPDIVO (CAP), OPDUALAG (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	15.3.24. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/X/0132 17.2.11. Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005 481/MEA 001
Sofia Trantza	Member	Greece	No interests declared	
Georgia Gkegka	Alternate	Greece	No interests declared	
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.1.1. Nivolumab – OPDIVO (CAP), OPDUALAG (CAP) 4.2.1. Ipilimumab – YERVOY (CAP) 6.1.2. Abatacept - ORENCIA (CAP) - PSUSA/000000 13/202212 15.3.24. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/X/0132 16.1.25. Lisocabtagene maraleucel, lisocabtagene maraleucel - BREYANZI (CAP) - PSUSA/000109 90/202302 16.2.2.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>Lenalidomide - LENALIDOMIDE ACCORD (CAP); LENALIDOMIDE KRKA (CAP); LENALIDOMIDE KRKA D.D. (SRD) (CAP); LENALIDOMIDE KRKA D.D. NOVO MESTO (CAP); LENALIDOMIDE MYLAN (CAP); REVLIMID (CAP); NAP - PSUSA/00001838/202212</p> <p>17.2.5. Deucravacitinib - SOTYKTU (CAP) - EMEA/H/C/005755/MEA 001</p> <p>17.2.11. Nivolumab, relatlimab - OPDUALAG (CAP) - EMEA/H/C/005481/MEA 001</p> <p>17.5.10. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 002.2</p>
Melinda Palfi	Alternate	Hungary	No interests declared	
Gudrun Þengilsdóttir	Alternate	Iceland	No restrictions applicable to this meeting	
Rhea Fitzgerald	Member	Ireland	No interests declared	
Eamon O Murchu	Alternate	Ireland	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Amelia Cupelli	Member	Italy	No interests declared	
Valentina Di Giovanni	Alternate	Italy	No interests declared	
Zane Neikena	Member	Latvia	No interests declared	
Zane Stade	Alternate	Latvia	No interests declared	
Lina Seibokiene	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain	Member	Luxembourg	No participation in final deliberations and voting on:	3.2.1.- EMA/H/A-31/1526
Anne-Cécile Vuillemin	Alternate	Luxembourg	No interests declared	
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	
Menno van der Elst	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	
David Olsen	Member	Norway	No participation in final deliberations and voting on:	3.2.1 – EMA/H/A-31/1526 6.1.4. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202301 16.1.19. Finerenone - KERENDIA (CAP) - PSUSA/00010978/202301 16.1.52. Vericiguat -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>VERQUVO (CAP) - PSUSA/00010950/202301</p> <p>16.3.17. Hypericum perforatum L., herba (NAP) - PSUSA/00001701/202301</p> <p>17.4.6. Radium (Ra223) - XOFIGO (CAP) - EMEA/H/C/002653/II/0052</p> <p>17.5.1. Aflibercept - EYLEA (CAP) - EMEA/H/C/002392/MEA 022</p> <p>17.5.13. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 005.5</p> <p>17.5.14. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.6</p>
Pernille Harg	Alternate	Norway	No interests declared	
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	
Irina Sandu	Alternate	Romania	No interests declared	
Anna Mareková	Member	Slovakia	No interests declared	
Miroslava Gocova	Alternate	Slovakia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Polona Golmajer	Member	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	
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	
Patricia McGettigan	Member	Independent scientific expert	No interests declared	
Tania Schink	Member	Independent scientific expert	No participation in final deliberations and voting on:	<p>7.3.1. Roflumilast – DAXAS (CAP) - EMEA/H/C/PSR /S/0041</p> <p>15.2.1. Acridinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002 706/WS2548/0 051; EKLIRA GENUAIR (CAP) - EMEA/H/C/002 211/WS2548/0 052</p> <p>15.2.2. Acridinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) -</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>EMA/H/C/003 969/WS2546/0039; DUAKLIR GENUAIR (CAP) - EMA/H/C/003 745/WS2546/0040</p> <p>17.2.15. Solriamfetol - SUNOSI (CAP) - EMA/H/C/004 893/MEA 002.3</p>
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	
Roberto Frontini	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messina	Alternate	Healthcare Professionals' Representative	No interests declared	
Petar Mas	Expert	Croatia	No interests declared	
Karin Erneholm	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul	Expert	Denmark	No interests declared	
Irene Krüger	Expert	Denmark	No interests declared	
Moritz Sander	Expert	Denmark	No interests declared	
Ane Blicher Schelde	Expert	Denmark	No restrictions applicable to this meeting	
Ditte Søgaard	Expert	Denmark	No interests declared	
Chau Minh Tran	Expert	Denmark	No interests declared	
Mette Wikkelsø	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
Thomas Berbain	Expert	France	No interests declared	
Camille de-Kervasdoue	Expert	France	No interests declared	
Vincent Gazin	Expert	France	No interests declared	
Youssef Shaim	Expert	France	No restrictions applicable to this meeting	
Anne Kleinau	Expert	Germany	No interests declared	
Larissa Kopp	Expert	Germany	No restrictions applicable to this meeting	
Dennis Lex	Expert	Germany	No interests declared	
Birte Niemann	Expert	Germany	No interests declared	
Susanne Winterscheid	Expert	Germany	No interests declared	
Orn Gudmundsson	Expert	Iceland	No interests declared	
Ragnhildur Heidarsdottir	Expert	Iceland	No interests declared	
Gareth Bowen	Expert	Ireland	No interests declared	
Niamh Buckley	Expert	Ireland	No interests declared	
Kevin Keohane	Expert	Ireland	No interests declared	
Evelyn Mulder-Olthof	Expert	Netherlands	No interests declared	
Paul ten Berg	Expert	Netherlands	No interests declared	
Monika Trojan	Expert	Poland	No interests declared	
Marta Marcelino	Expert	Portugal	No interests declared	
Carla Torre	Expert	Portugal	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Natividad Galiana	Expert	Spain	No restrictions applicable to this meeting	
Luz Medrano	Expert	Spain	No interests declared	
Charlotte Backman	Expert	Sweden	No interests declared	
Oscar Ljungberg	Expert	Sweden	No interests declared	
Karin Nylén	Expert	Sweden	No interests declared	
Christin Olofsson	Expert	Sweden	No restrictions applicable to this meeting	
Martina Raud	Expert	Sweden	No interests declared	
Linnea Willden Melin	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				
<i>Experts were evaluated against the agenda topics or activities they participated in.</i>				

20. Annex III - List of acronyms and abbreviations

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

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

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>