



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 11-14 April 2023

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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



Table of contents

1.	Introduction	12
1.1.	Welcome and declarations of interest of members, alternates and experts.....	12
1.2.	Agenda of the meeting on 11-14 April 2023	12
1.3.	Minutes of the previous meeting on 13-16 March 2023	12
2.	EU referral procedures for safety reasons: urgent EU procedures	12
2.1.	Newly triggered procedures	12
2.2.	Ongoing procedures	12
2.3.	Procedures for finalisation	13
3.	EU referral procedures for safety reasons: other EU referral procedures	13
3.1.	Newly triggered procedures	13
3.2.	Ongoing procedures	13
3.3.	Procedures for finalisation	13
3.4.	Re-examination procedures.....	13
3.5.	Others	13
4.	Signals assessment and prioritisation	13
4.1.	New signals detected from EU spontaneous reporting systems.....	13
4.1.1.	Enoxaparin – INHIXA (CAP)	13
4.2.	New signals detected from other sources.....	14
4.3.	Signals follow-up and prioritisation.....	14
4.3.1.	Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/113	14
4.3.2.	Elasomeran – SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/081	15
4.3.3.	Evolocumab – REPATHA (CAP) - EMEA/H/C/003766/SDA/017	15
4.3.4.	Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide – XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); insulin glargine, lixisenatide – SULIQUA (CAP); lixisenatide - LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP)	16
4.3.5.	Tozinameran – COMIRNATY (CAP) - EMEA/H/C/005735/SDA/061	17
4.4.	Variation procedure(s) resulting from signal evaluation	17
5.	Risk management plans (RMPs)	17
5.1.	Medicines in the pre-authorisation phase.....	17
5.1.1.	Natalizumab - EMEA/H/C/005752	18
5.1.2.	Respiratory syncytial virus vaccines - EMEA/H/C/006027.....	18
5.1.3.	Talquetamab - EMEA/H/C/005864, PRIME, Orphan	18

5.2.	Medicines in the post-authorisation phase – PRAC-led procedures	18
5.3.	Medicines in the post-authorisation phase – CHMP-led procedures.....	18
5.3.1.	Nintedanib - OFEV (CAP) - EMEA/H/C/003821/X/0052/G	18
6.	Periodic safety update reports (PSURs)	19
6.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only.....	19
6.1.1.	Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202209.....	19
6.1.2.	Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/202209	20
6.1.3.	Amikacin - ARIKAYCE LIPOSOMAL (CAP) - PSUSA/00010882/202209.....	20
6.1.4.	Bupivacaine, meloxicam - ZYNRELEF (CAP) - PSUSA/00010880/202209.....	21
6.1.5.	Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202209	22
6.1.6.	Coronavirus (COVID-19) vaccine (Ad26.COVS-2, recombinant) - JCOVDEN (CAP) - PSUSA/00010916/202208	23
6.1.7.	Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202209	24
6.1.8.	Infliximab - FLIXABI (CAP); INFLECTRA (CAP); REMICADE (CAP); REMSIMA (CAP); ZESSLY (CAP) - PSUSA/00010759/202208	24
6.1.9.	Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/202209	25
6.1.10.	Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/202209	26
6.1.11.	Ponesimod - PONVORY (CAP) - PSUSA/00010940/202209	27
6.1.12.	Pralsetinib - GAVRETO (CAP) - PSUSA/00010961/202209.....	28
6.1.13.	Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/202208	29
6.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	29
6.2.1.	Midazolam - BUCCOLAM (CAP); NAP - PSUSA/00010118/202209.....	29
6.2.2.	Pantoprazole - CONTROLLOC CONTROL (CAP); PANTOZOL CONTROL (CAP); SOMAC CONTROL (CAP); NAP - PSUSA/00002285/202208	30
6.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only	31
6.3.1.	Adenosine (NAP) - PSUSA/00000062/202208	31
6.3.2.	Midazolam (NAP) - PSUSA/00002057/202209	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
7.1.1.	Fosdenopterin - NULIBRY (CAP) - EMEA/H/C/PSP/S/0103	33
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	34
7.2.1.	Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/MEA 002.....	34
7.2.2.	Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.2.....	35
7.3.	Results of PASS imposed in the marketing authorisation(s).....	35

7.4.	Results of PASS non-imposed in the marketing authorisation(s)	35
7.4.1.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0092	35
7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation	36
7.5.1.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.8	36
7.6.	Others	37
7.7.	New Scientific Advice	37
7.8.	Ongoing Scientific Advice	37
7.9.	Final Scientific Advice (Reports and Scientific Advice letters)	37
8.	Renewals of the marketing authorisation, conditional renewal and annual reassessments	37
8.1.	Annual reassessments of the marketing authorisation	37
8.1.1.	Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0045 (without RMP)	37
8.2.	Conditional renewals of the marketing authorisation	38
8.3.	Renewals of the marketing authorisation	38
9.	Product related pharmacovigilance inspections	38
9.1.	List of planned pharmacovigilance inspections	38
9.2.	Ongoing or concluded pharmacovigilance inspections	38
9.3.	Others	38
10.	Other safety issues for discussion requested by CHMP or EMA	38
10.1.	Safety related variations of the marketing authorisation	38
10.2.	Timing and message content in relation to Member States' safety announcements	38
10.3.	Other requests	39
10.4.	Scientific Advice	39
11.	Other safety issues for discussion requested by the Member States	39
11.1.	Safety related variations of the marketing authorisation	39
11.2.	Other requests	39
12.	Organisational, regulatory and methodological matters	39
12.1.	Mandate and organisation of PRAC	39
12.1.1.	PRAC membership	39
12.1.2.	Vote by proxy	39
12.2.	Coordination with EMA Scientific Committees or CMDh-v	39
12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	39
12.4.	Cooperation within the EU regulatory network	39
12.4.1.	Coronavirus (COVID-19) pandemic - update	39
12.5.	Cooperation with International Regulators	40

12.6.	Contacts of PRAC with external parties and interaction with the Interested Parties to the Committee.....	40
12.7.	PRAC work plan.....	40
12.8.	Planning and reporting.....	40
12.8.1.	Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q1 2023.....	40
12.9.	Pharmacovigilance audits and inspections.....	40
12.9.1.	Pharmacovigilance systems and their quality systems.....	40
12.9.2.	Pharmacovigilance inspections.....	40
12.9.3.	Pharmacovigilance audits.....	40
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list.....	40
12.10.1.	Periodic safety update reports.....	40
12.10.2.	Granularity and Periodicity Advisory Group (GPAG).....	41
12.10.3.	PSURs repository.....	41
12.10.4.	Union reference date list – consultation on the draft list.....	41
12.11.	Signal management.....	41
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group.....	41
12.12.	Adverse drug reactions reporting and additional monitoring.....	41
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	41
12.12.2.	Additional monitoring.....	41
12.12.3.	List of products under additional monitoring – consultation on the draft list.....	41
12.13.	EudraVigilance database.....	42
12.13.1.	Activities related to the confirmation of full functionality.....	42
12.14.	Risk management plans and effectiveness of risk minimisations.....	42
12.14.1.	Risk management systems.....	42
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations.....	42
12.14.3.	Risk management plan (RMP) of medicinal product(s) - publication on EMA website.....	42
12.15.	Post-authorisation safety studies (PASS).....	42
12.15.1.	Post-authorisation Safety Studies – imposed PASS.....	42
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS.....	42
12.16.	Community procedures.....	42
12.16.1.	Referral procedures for safety reasons.....	42
12.16.2.	Lessons learned on referral procedures – case study.....	43
12.17.	Renewals, conditional renewals, annual reassessments.....	43
12.18.	Risk communication and transparency.....	43
12.18.1.	Public participation in pharmacovigilance.....	43
12.18.2.	Safety communication.....	43
12.19.	Continuous pharmacovigilance.....	43

12.19.1.	Incident management	43
12.20.	Impact of pharmacovigilance activities	43
12.20.1.	Study on the impact of EU label changes for fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends - follow-up discussion on PRAC Sponsors' assessment	43
12.21.	Others	43
12.21.1.	EMA expert management systems update on the new Experts Management Tool	43
12.21.2.	PRAC drafting group on the risks of dependence and addiction of opioids - update.....	44
12.21.3.	EMA policy on handling of competing interests for scientific committees' members and experts – revision of policy 0044	44
12.21.4.	EMA Stakeholder meeting - European Federation of Pharmaceutical Industries and Associations (EFPIA) study report on 'Industry perspective on post-authorisation safety study (PASS)' (2016-2022)	44
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.	Acetazolamide (NAP)	45
14.1.2.	Apalutamide – ERLEADA (CAP).....	45
14.1.3.	Megestrol (NAP)	45
14.1.4.	Pramipexole – MIRAPEXIN (CAP); OPRYMEA (CAP); PRAMIPEXOLE TEVA (CAP); SIFROL (CAP); (NAP)	46
14.2.	New signals detected from other sources.....	46
15.	Annex I – Risk management plans	46
15.1.	Medicines in the pre-authorisation phase.....	46
15.1.1.	Degarelix acetate - EMEA/H/C/006048	46
15.1.2.	Pegfilgrastim - EMEA/H/C/005587	46
15.2.	Medicines in the post-authorisation phase – PRAC-led procedures	46
15.2.1.	Efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/II/0130	46
15.2.2.	Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0017, Orphan	46
15.2.3.	Palivizumab - SYNAGIS (CAP) - EMEA/H/C/000257/II/0131	47
15.2.4.	Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0077	47
15.2.5.	Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS2402/0069; MODIGRAF (CAP) - EMEA/H/C/000954/WS2402/0045	47
15.2.6.	Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0059	47
15.2.7.	Tecovirimat - TECOVIRIMAT SIGA (CAP) - EMEA/H/C/005248/II/0006	48
15.2.8.	Tobramycin - TOBI PODHALER (CAP) - EMEA/H/C/002155/II/0053, Orphan	48
15.2.9.	Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0061	48
15.3.	Medicines in the post-authorisation phase – CHMP-led procedures.....	48
15.3.1.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0094	48
15.3.2.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0095	48

15.3.3.	Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0077/G	49
15.3.4.	Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0022, Orphan	49
15.3.5.	Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0023, Orphan	49
15.3.6.	Azacitidine - AZACITIDINE ACCORD (CAP) - EMEA/H/C/005147/X/0013	50
15.3.7.	Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0002	50
15.3.8.	Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2421/0059; FORXIGA (CAP) - EMEA/H/C/002322/WS2421/0080	50
15.3.9.	Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - EMEA/H/C/004554/II/0025	50
15.3.10.	Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/II/0097/G	51
15.3.11.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/II/0076	51
15.3.12.	Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/II/0037/G	51
15.3.13.	Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0011/G, Orphan	52
15.3.14.	Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/II/0019	52
15.3.15.	Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0100	52
15.3.16.	Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0114/G	52
15.3.17.	Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/X/0033, Orphan ..	53
15.3.18.	Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123	53
15.3.19.	Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0052	53
15.3.20.	Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0078/G	54
15.3.21.	Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0039	54
15.3.22.	Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0125/G	54
15.3.23.	Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan	54
15.3.24.	Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0064, Orphan	55
15.3.25.	Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0037	55
15.3.26.	Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/II/0020	55
15.3.27.	Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0054/G, Orphan	56
15.3.28.	Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0042	56
15.3.29.	Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076	56
15.3.30.	Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0114	56
15.3.31.	Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0096	57
15.3.32.	Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0009	57

16. Annex I - Periodic safety update reports (PSURs) 57

16.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	58
16.1.1.	Abrocitinib - CIBINQO (CAP) - PSUSA/00010976/202209	58
16.1.2.	Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202209	58
16.1.3.	Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202209	58
16.1.4.	Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202209	58
16.1.5.	Cholic acid - ORPHACOL (CAP) - PSUSA/00010208/202209	58

16.1.6.	Copper (64Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/202208	58
16.1.7.	Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/202208.....	58
16.1.8.	Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202209.....	59
16.1.9.	Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202209.....	59
16.1.10.	Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202209.....	59
16.1.11.	Ebola vaccine (rDNA, replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202209	59
16.1.12.	Eliglustat - CERDELGA (CAP) - PSUSA/00010351/202208.....	59
16.1.13.	Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202209	59
16.1.14.	Fremanezumab - AJOVY (CAP) - PSUSA/00010758/202209	59
16.1.15.	Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202209	60
16.1.16.	Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202209	60
16.1.17.	Human alfa1-proteinase inhibitor - RESPREEZA (CAP) - PSUSA/00010410/202208	60
16.1.18.	Idebenone - RAXONE (CAP) - PSUSA/00010412/202209	60
16.1.19.	Insulin aspart - FIASP (CAP); INSULIN ASPART SANOFI (CAP); KIRSTY (CAP); NOVOMIX (CAP); NOVORAPID (CAP); TRUVELOG MIX 30 (CAP) - PSUSA/00001749/202209	60
16.1.20.	Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202209.....	60
16.1.21.	Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202209.....	61
16.1.22.	Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202209	61
16.1.23.	Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/202209.....	61
16.1.24.	Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202209	61
16.1.25.	Olipudase alfa - XENPOZYME (CAP) - PSUSA/00011003/202209.....	61
16.1.26.	Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202209	61
16.1.27.	Pitolisant - OZAWADE (CAP); WAKIX (CAP) - PSUSA/00010490/202209.....	61
16.1.28.	Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/202209	62
16.1.29.	Rilpivirine - REKAMBYS (CAP) - PSUSA/00010901/202209.....	62
16.1.30.	Ritonavir - NORVIR (CAP) - PSUSA/00002651/202208	62
16.1.31.	Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202209.....	62
16.1.32.	Tebentafusp - KIMMTRAK (CAP) - PSUSA/00010991/202209	62
16.1.33.	Tenecteplase - METALYSE (CAP) - PSUSA/00002888/202208.....	62
16.1.34.	Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202209.....	62
16.1.35.	Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202209	63
16.1.36.	Trabectedin - YONDELIS (CAP) - PSUSA/00003001/202209.....	63
16.1.37.	Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202209	63
16.1.38.	Vernakalant hydrochloride - BRINAVESS (CAP) - PSUSA/00003109/202208	63
16.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	63
16.2.1.	Budesonide, formoterol - BIRESP SPIROMAX (CAP); BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP); DUORESP SPIROMAX (CAP); NAP - PSUSA/00010585/202208	63
16.2.2.	Glycopyrronium - SIALANAR (CAP); NAP - PSUSA/00010529/202209	63

16.2.3.	Octocog alfa - ADVATE (CAP); KOGENATE BAYER (CAP); KOVALTRY (CAP); NAP - PSUSA/00002200/202208	64
16.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only	64
16.3.1.	Allergen for therapy: dermatophagoides pteronyssinus, dermatophagoides farina (NAP) - PSUSA/00010582/202209	64
16.3.2.	Biperiden (NAP) - PSUSA/00000415/202208.....	64
16.3.3.	Choline alfoscerate (NAP) - PSUSA/00010599/202208	64
16.3.4.	Dexamfetamine (NAP) - PSUSA/00000986/202209.....	64
16.3.5.	Dornase alpha (NAP) - PSUSA/00001164/202209.....	64
16.3.6.	Drospirenone, ethinylestradiol (NAP) - PSUSA/00010217/202209.....	65
16.3.7.	Fluoxetine (NAP) - PSUSA/00001442/202209	65
16.3.8.	Fluvastatin (NAP) - PSUSA/00001457/202208	65
16.3.9.	Human tetanus immunoglobulin (NAP) - PSUSA/00002909/202208	65
16.3.10.	Minocycline (NAP) - PSUSA/00002065/202208.....	65
16.3.11.	Paricalcitol (NAP) - PSUSA/00002316/202208.....	65
16.3.12.	Piperacillin, tazobactam (NAP) - PSUSA/00002425/202209.....	65
16.3.13.	Tretinoin (NAP) - PSUSA/00003016/202208	66
16.3.14.	Treosulfan (NAP) - PSUSA/00009319/202208	66
16.4.	Follow-up to PSUR/PSUSA procedures	66
16.5.	Variation procedure(s) resulting from PSUSA evaluation	66
16.5.1.	Fondaparinux sodium - ARIXTRA (CAP) - EMEA/H/C/000403/II/0087	66
16.6.	Expedited summary safety reviews	66
17.	Annex I – Post-authorisation safety studies (PASS)	66
17.1.	Protocols of PASS imposed in the marketing authorisation(s)	66
17.1.1.	Evinacumab - EVKEEZA (CAP) - EMEA/H/C/PSA/S/0098.1	66
17.1.2.	Valproate (NAP) - EMEA/H/N/PSP/J/0074.6	67
17.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	67
17.2.1.	Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/MEA 002.2	67
17.2.2.	Ciltacabtagene autoleucel - CARVYKTI (CAP) - EMEA/H/C/005095/MEA 007.1	67
17.2.3.	Elasomeran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065.2	67
17.2.4.	Pitolisant - OZAWADE (CAP) - EMEA/H/C/005117/MEA 003	68
17.2.5.	Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 002	68
17.2.6.	Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 005	68
17.2.7.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 062.....	68
17.3.	Results of PASS imposed in the marketing authorisation(s).....	69
17.4.	Results of PASS non-imposed in the marketing authorisation(s)	69
17.4.1.	Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0031.....	69

17.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation	69
17.5.1.	Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.8	69
17.5.2.	Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.4	69
17.5.3.	Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/MEA 035	69
17.5.4.	Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.10	70
17.5.5.	Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.5	70
17.5.6.	Rurioctocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/ANX 002.2	70
17.5.7.	Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.6	70
17.6.	Others	70
17.6.1.	Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.5	70
17.6.2.	Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.4	71
17.7.	New Scientific Advice	71
17.8.	Ongoing Scientific Advice	71
17.9.	Final Scientific Advice (Reports and Scientific Advice letters)	71
18.	Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments	71
18.1.	Annual reassessments of the marketing authorisation	71
18.1.1.	Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0045 (without RMP) ...	71
18.1.2.	Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/S/0020 (without RMP)	72
18.2.	Conditional renewals of the marketing authorisation	72
18.2.1.	Belantamab mafodotin - BLENREP (CAP) - EMEA/H/C/004935/R/0017 (with RMP)	72
18.2.2.	Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/R/0024 (without RMP)	72
18.2.3.	Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0015 (without RMP)	72
18.2.4.	Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/R/0029 (without RMP)	72
18.2.5.	Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0014 (without RMP)	72
18.2.6.	Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/R/0015 (without RMP)	73
18.2.7.	Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/R/0003 (without RMP)	73
18.3.	Renewals of the marketing authorisation	73
18.3.1.	Abemaciclib - VERZENIOS (CAP) - EMEA/H/C/004302/R/0025 (without RMP)	73
18.3.2.	Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/R/0024 (without RMP)	73
18.3.3.	Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/R/0021 (with RMP)	73
18.3.4.	Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/R/0027 (without RMP)	73
18.3.5.	Deferiprone - DEFERIPRONE LIPOMED (CAP) - EMEA/H/C/004710/R/0011 (with RMP)	73
18.3.6.	Doravirine - PIFELTRO (CAP) - EMEA/H/C/004747/R/0027 (without RMP)	74
18.3.7.	Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - EMEA/H/C/004746/R/0034 (without RMP)	74
18.3.8.	Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/R/0029 (without RMP)	74

18.3.9.	Gefitinib - GEFITINIB MYLAN (CAP) - EMEA/H/C/004826/R/0008 (without RMP)	74
18.3.10.	Lenalidomide - LENALIDOMIDE ACCORD (CAP) - EMEA/H/C/004857/R/0021 (without RMP)	74
18.3.11.	Pegfilgrastim - PELGRAZ (CAP) - EMEA/H/C/003961/R/0040 (with RMP)	74
18.3.12.	Pegfilgrastim - ZIEXTENZO (CAP) - EMEA/H/C/004802/R/0025 (with RMP).....	74
18.3.13.	Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0046 (without RMP).....	75
18.3.14.	Vigabatrin - KIGABEQ (CAP) - EMEA/H/C/004534/R/0012 (with RMP)	75
18.3.15.	Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/R/0027 (with RMP)	75
19.	Annex II – List of participants	75
20.	Annex III - List of acronyms and abbreviations	83
21.	Explanatory notes	84

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 in-person with some members connected 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. Tania Schink declared a new competing interest regarding solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.2. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.3](#)). All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

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

1.2. Agenda of the meeting on 11-14 April 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 13-16 March 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 13-16 March 2023 were published on the EMA website on 22 June 2023 ([EMA/PRAC/236189/2023](#)).

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

None

3.3. Procedures for finalisation

None

3.4. Re-examination procedures¹

None

3.5. Others

None

4. Signals assessment and prioritisation²

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1.

4.1.1. Enoxaparin – INHIXA (CAP)

Applicant: Techdow Pharma

PRAC Rapporteur: Menno van der Elst

Scope: Signal of angiokeratoma

EPITT 19909 – New signal

Background

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

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

² Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

During routine signal detection activities, a signal of angiokeratoma was identified by EMA, based on 4 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from EudraVigilance and scientific literature, PRAC agreed that the signal should be further assessed.

Summary of recommendation(s)

- In the next PSUR³, the MAHs for enoxaparin-containing products should submit to EMA a cumulative review of cases of angiokeratoma, together with a proposal for amending the product information and/or RMP, as warranted.

4.2. New signals detected from other sources

None

4.3. Signals follow-up and prioritisation

4.3.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/SDA/113

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Signal of pemphigus and pemphigoid

EPITT 19858 – Follow-up to December 2022⁴

Background

For background information, see [PRAC minutes December 2022](#).

The Marketing Authorisation Holder (MAH) replied to the request for information on the signal of pemphigus and pemphigoid, and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the real-world data analysis performed by EMA, PRAC agreed that the current evidence is insufficient to establish a causal relationship between Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) and pemphigus or pemphigoid. Hence, PRAC agreed that no further action is deemed warranted at this stage.

Summary of recommendation(s)

- The MAH for Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant])) should continue to closely monitor any new cases of pemphigus and/or pemphigoid in the next PSURs.

See [EMA/PRAC/164741/2023](#) published on 8 May 2023 on the EMA website.

³ Data lock point (DLP) 03 April 2024

⁴ Held 28 November - 01 December 2022

4.3.2. Elasoameran – SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/081

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of pemphigus and pemphigoid

EPITT 19860 – Follow-up to December 2022⁵

Background

For background information, see [PRAC minutes December 2022](#).

The Marketing Authorisation Holder (MAH) replied to the request for information on the signal of pemphigus and pemphigoid, and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the real-world data analysis performed by EMA, PRAC agreed that the current evidence is insufficient to establish a causal relationship between Spikevax (elasoameran) and pemphigus or pemphigoid. Hence, PRAC agreed that no further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR⁶, the MAH for Spikevax (elasoameran) should submit to EMA a separate review of all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid, including data from clinical trials, post-marketing exposure and scientific literature, together with a causality assessment and an observed versus expected (O/E) analysis.

See [EMA/PRAC/164741/2023](#) published on 8 May 2023 on the EMA website.

4.3.3. Evolocumab – REPATHA (CAP) - EMEA/H/C/003766/SDA/017

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of weight increase and abnormal weight gain

EPITT 19867 – Follow-up to December 2022⁷

Background

For background information, see [PRAC minutes December 2022](#).

The Marketing Authorisation Holder (MAH) replied to the request for information on the signal of weight increase and abnormal weight gain and the responses were assessed by the Rapporteur.

Discussion

⁵ Held 28 November - 01 December 2022

⁶ Data lock point (DLP) 17 June 2023

⁷ Held 28 November - 01 December 2022

Having considered the available evidence in EudraVigilance and the MAH's responses, PRAC concluded that the current evidence is insufficient to establish a causal relationship between Repatha (evolocumab) and abnormal weight gain and weight increased.

Summary of recommendation(s)

- The MAH for Repatha (evolocumab) should continue to monitor cases of abnormal weight gain and weight increased as part of routine safety surveillance.

See [EMA/PRAC/164741/2023](#) published on 8 May 2023 on the EMA website.

4.3.4. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide – XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); insulin glargine, lixisenatide – SULIQUA (CAP); lixisenatide - LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP)

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

PRAC Rapporteur: Mari Thorn

Scope: Signal of thyroid cancer

EPITT 18292 – Follow up to January 2023

Background

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

Discussion

Having considered the available evidence from the publication by *Bezin et al*⁸, as well as the meta-analyses by *Hu et al*⁹ and *Alves et al*¹⁰, PRAC agreed that further evaluation of the signal of thyroid cancer with 4lucagon-like peptide-1 (GLP-1) receptor agonists is warranted.

Summary of recommendation(s)

- The MAHs for Victoza (liraglutide), Saxenda (liraglutide), Xultophy (insulin degludec, liraglutide), Ozempic (semaglutide), Rybelsus (semaglutide), Wegovy (semaglutide), Bydureon (exenatide), Byetta (exenatide), Trulicity (dulaglutide), Lyxumia (lixisenatide) and Suliqua (insulin glargine, lixisenatide) should submit to EMA, within 90 days, responses to the adopted LoQs. The MAHs should discuss the publications by *Bezin et al*, *Hu et al*. and *Alves et al.*, as well as any other available data (including non-clinical data, clinical data and literature) on the potentially increased risk of thyroid cancer associated with their respective medicinal products. The MAHs should propose updates of the product information and/or RMP as warranted. In addition, the MAHs should discuss if there is need for additional risk minimisation measures and/or pharmacovigilance activities to further characterize this risk.

See [EMA/PRAC/164741/2023](#) published on 8 May 2023 on the EMA website.

⁸ Bezin et al. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. *Bezin et al.* 2022 *Diabetes Care*. 2022 Nov 10; dc221148. doi: 10.2337/dc22-1148. (Online ahead of print)

⁹ Hu W, Song R, Cheng R, Liu C, Guo R, Tang W, Zhang J, Zhao Q, Li X, Liu J Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)*. 2022 Jul 11;13:927859

¹⁰ Alves C, Batel-Marques F, Macedo AF A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer, *Diabetes Res Clin Pract* 2012 Nov;98(2):271-84

4.3.5. Tozinameran – COMIRNATY (CAP) - EMEA/H/C/005735/SDA/061

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pemphigus and pemphigoid

EPITT 19859 – Follow-up to December 2022¹¹

Background

For background information, see [PRAC minutes December 2022](#).

The Marketing Authorisation Holder (MAH) replied to the request for information on the signal of pemphigus and pemphigoid, and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the real-world data analysis performed by EMA, PRAC agreed that the current evidence is insufficient to establish a causal relationship between Comirnaty (tozinameran) and pemphigus or pemphigoid. Hence, PRAC agreed that no further action is deemed warranted at this stage.

Summary of recommendation(s)

- In the next PSUR¹², the MAH for Comirnaty (tozinameran) should submit to EMA a separate review of all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid, including data from clinical trials, post-marketing exposure and scientific literature, together with a causality assessment and an observed versus expected (O/E) analysis.

See [EMA/PRAC/164741/2023](#) published on 8 May 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 pages for upcoming information (<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>).

See also Annex I 15.1.

¹¹ Held 28 November - 01 December 2022

¹² Data lock point (DLP) 18 June 2023

5.1.1. Natalizumab - EMEA/H/C/005752

Scope: Treatment of active relapsing remitting multiple sclerosis (RRMS)

5.1.2. Respiratory syncytial virus vaccines - EMEA/H/C/006027

Scope (accelerated assessment): Prevention of respiratory tract disease

5.1.3. Talquetamab - EMEA/H/C/005864, PRIME, Orphan

Applicant: Janssen-Cilag International N.V.

Scope: (accelerated assessment): Monotherapy treatment of adult patients with relapsed and refractory multiple myeloma

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

See Annex I 15.2.

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

See also Annex I 15.3.

5.3.1. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/X/0052/G

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension application to add a new strength of 25 mg soft capsule grouped with a type II variation to add a new indication of treatment of fibrosing Interstitial Lung Diseases (ILDs) in children and adolescents from 6 to 17 years of age, based on results from study 1199 0337 (InPedILD); a randomised, placebo-controlled, double-blind, multicentre, multinational, phase III clinical trial undertaken to evaluate dose-exposure and safety of nintedanib on top of standard of care in children and adolescents (6 to 17 years old) with clinically significant fibrosing ILD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes to the list of local representatives in the package leaflet. The updated RMP version 12.0 is also submitted

Background

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

CHMP is evaluating an extension application for Ofev a centrally authorised product containing nintedanib, to add a new strength of 25 mg soft capsule, as well as to add a new indication of treatment of fibrosing interstitial lung diseases (ILDs) in children and adolescents from 6 to 17 years of age, based on results from study 1199 0337 (InPedILD). 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 January 2023](#).

Summary of advice

- The RMP for Ofev (nintedanib) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 10 is submitted.
- PRAC considered that the risk of off-label use in the paediatric population should be addressed by implementing routine risk minimisation measures (RMMs) (update of the product information advising against use in the paediatric population) due to additional safety concerns identified, particularly related to growth and development. Therefore, the MAH should include the risks associated with off-label use in the paediatric population as important potential risk in the RMP and propose appropriate RMMs and pharmacovigilance activities in order to address this safety concern. Moreover, PRAC supported that the safety data in the paediatric population should be clearly mentioned in the product information. Considering the above, PRAC considered that longer safety data would ideally be collected to address long term safety in the paediatric population.

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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202209

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

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 Verzenios, a centrally authorised medicine containing abemaciclib 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 Verzenios (abemaciclib) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should submit cumulative reviews of cases of retinal disorders and corneal disorders, including data from clinical trials and post-marketing experience. In addition, the MAH should provide a cumulative review of cases of acute kidney injury, including data from clinical trials and post-marketing setting retrieved by 'acute renal failure' broad standardised MedDRA¹³ queries (SMQ), as well as from

¹³ Medical Dictionary for Regulatory Activities

scientific literature, including the publication by *Gupta et al*¹⁴. The MAH should also include a discussion on the possible biological mechanisms, especially in the context of a potential class effect and propose an update to the product information as warranted.

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

6.1.2. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/202209

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

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 Lemtrada, a centrally authorised medicine containing alemtuzumab 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 Lemtrada (alemtuzumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add alopecia areata as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.

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

6.1.3. Amikacin¹⁶ - ARIKAYCE LIPOSOMAL (CAP) - PSUSA/00010882/202209

Applicant: Insméd Netherlands B.V.

PRAC Rapporteur: Jean-Michel Dogné

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.

¹⁴ Gupta S et al. Clinicopathologic features of acute kidney injury associated with CDK4/6 inhibitors. *Kidney international reports* 2022 7;618-23

¹⁵ 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.

¹⁶ Centrally authorised product(s) only

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Arikayce liposomal, a centrally authorised medicine containing amikacin 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 Arikayce liposomal (amikacin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial rRNA mutations' as a warning. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁷.
- In the next PSUR, the MAH should provide a cumulative review of serious cases of vocal cord disorder, vocal cord inflammation, laryngitis, dysphonia and aphonia, as well as of laryngeal ulceration. In addition, the MAH should specifically monitor Lamira Nebulizer System device-related issues (improper functioning or incorrect use of the device) leading to deviations from the recommended dosage regimen of amikacin liposome inhalation suspension (ALIS), in light of underdosing and the associated risk of antimicrobial resistance.

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. Bupivacaine, meloxicam - ZYNRELEF (CAP) - PSUSA/00010880/202209

Applicant: Heron Therapeutics, B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

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 Zynrelef, a centrally authorised medicine containing bupivacaine/meloxicam 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 Zynrelef (bupivacaine/meloxicam) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing wording on use during pregnancy, based on the PRAC advice for non-steroidal anti-inflammatory drugs (NSAID)-containing medicinal products (see [PRAC minutes July 2022](#)), as well as

¹⁷ 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.

the wording on use during lactation based on the results of study HTX-011-220¹⁸. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.

- In the next PSUR, with regard to the important potential risk of wound healing impairment, the MAH should include the MedDRA PT²⁰ 'wound dehiscence' when discussing new information regarding wound healing impairment.

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. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202209

Applicant: Regeneron Ireland Designated Activity Company (DAC)

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 Libtayo, a centrally authorised medicine containing cemiplimab 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 Libtayo (cemiplimab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add haemophagocytic lymphohistiocytosis as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should discuss the publication by *Han et al.*²² and propose to update the product information as warranted.
- With the next regulatory opportunity, the MAH should propose an updated version of the key elements of the patient card covering all the relevant and important key elements to mitigate the important identified risk 'immune-related adverse reactions'. The updated patient card would therefore replace the current available educational materials (including patient guide).

¹⁸ phase 2, open-label study of the PK and safety of HTX-011 administered postpartum to women undergoing a planned caesarean section

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

²⁰ Preferred term

²¹ Update of SmPC sections 4.2, 4.4. and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

²² Han CY, Fitzgerald C, Lee M, et al. Association Between Toxic Effects and Survival in Patients With Cancer and Autoimmune Disease Treated With Checkpoint Inhibitor Immunotherapy [published online ahead of print, 2022 Jul 7]. *JAMA Oncol.* 2022;e222081. doi:10.1001/jamaoncol.2022.2081

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

6.1.6. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - JCOVDEN (CAP) - PSUSA/00010916/202208

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

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 Jcovden, a centrally authorised medicine containing coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Jcovden (Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant)) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, by 17 April 2023, a variation to address their proposal to add myo-/peri-carditis as important identified risk in the RMP, including detailed analyses of available safety data on this topic, a discussion on the benefit-risk balance of this vaccine taking these new safety data into account and in relation to the current knowledge of safety and efficacy, as well as the epidemiological evolution of the SARS-CoV-2 virus. The MAH should discuss the need for an update of the product information and/or RMP as warranted.
- In the next PSUR, the MAH should discuss the risk for postural orthostatic tachycardia syndrome (POTS) after Covid-19 vaccination as per publication by *Kwan et al*²³. Furthermore, the MAH should provide a review of cases of severe cutaneous adverse reactions (SCARs) including data from post-marketing setting and literature.

The PRAC recommendation is without prejudice to the outcome of the requested variation.

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.

²³ Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. *Nat Cardiovasc Res* (2022)

6.1.7. Idecabtagene vicleucel - ABECMA (CAP) - PSUSA/00010954/202209

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP²⁴

PRAC Rapporteur: Ulla Wändel Liminga

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 Abecma, a centrally authorised medicine containing idecabtagene vicleucel 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 Abecma (idecabtagene vicleucel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add parkinsonism as a warning and as an undesirable effect. Therefore, the current terms of the marketing authorisation(s) should be varied²⁵.
- In the next PSUR, the MAH should provide a cumulative review of cases suspicious for immune effector cell-associated neurotoxicity syndrome (ICANS), including cases reporting aphasia, dysgraphia or apraxia. The MAH should also discuss the need for an update of the product information as warranted. Finally, the MAH should provide more detailed updates about the registry-based PASS (BB2121-MM-006) progress, including the fraction of patients treated in EU and captured in the EBMT registry, data completeness and availability of patient-level data.

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

6.1.8. Infliximab - FLIXABI (CAP); INFLECTRA (CAP); REMICADE (CAP); REMSIMA (CAP); ZESSLY (CAP) - PSUSA/00010759/202208

Applicant(s): Samsung Bioepis NL B.V. (Flixabi), Pfizer Europe MA EEIG (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft. (Remsima), Sandoz GmbH (Zessly)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

²⁴ Advanced therapy medicinal product

²⁵ Update of SmPC sections 4.4. and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

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 Flixabi, Inflectra, Remicade, Remsima and Zessly, centrally authorised medicines containing infliximab 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 the following infliximab-containing products Flixabi, Inflectra, Remicade, Remsima and Zessly, in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH for Remicade (infliximab) should submit to EMA, within 4 months, a cumulative review of cases of weight gain based on data from clinical trials, observational studies and literature. The MAH should also discuss the need for an update of the product information as warranted.
- In the next PSUR, the MAHs should provide a cumulative review of cases of cancer of the urinary tract and of bone malignancy in paediatric patients from data of clinical trials, other observational studies, post-marketing experience and the literature, as well as a discussion on plausible mechanisms. The MAHs should also provide a review of cases of suicide ideas/suicide attempts/completed suicides from clinical trials and post-authorisation safety studies (PASS), as well as a literature review of cases of severe psychiatric disorders and suicide. Finally, the MAHs should also discuss the need for an update of the product information as warranted.

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

6.1.9. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/202209

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion 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 Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to add severe cutaneous adverse reactions (SCARs) including acute generalised exanthematous pustulosis (AGEP) as a warning and to add AGEP as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.
- The MAH should submit to EMA, within 30 days, a variation in order to enhance the existing risk minimisation measures (RMMs) on the risk of concurrent use of opioids with Mysimba, including a comprehensive proposal to update and streamline the relevant wording on opioids in the product information. In addition, the MAH should specify the opioid-free interval prior to starting naltrexone/bupropion treatment more precisely. The MAH should discuss possible further measures to address this risk. Furthermore, the MAH should clarify the current recommendation in the package leaflet that a blood test (referring to opioids) may be carried out prior to starting treatment with Mysimba (naltrexone, bupropion) and whether the SmPC should be updated accordingly.
- In the next PSUR, the MAH should provide cumulative reviews of serious cases of gastrointestinal disorders (nausea, vomiting), of cases of apathy, of cases in patients with hepatic impairment and renal impairment including an evaluation of the adherence to RMMs in place, of cases with long-term use selected by the time to onset of ADRs (>1 year), of cases related to fall, injury and fractures, along with a discussion whether the risk is increased in elderly, of cases of interactions with other anti-obesity drugs (such as semaglutide) and 5-HT3 antagonists, and of cases of anaphylactic reaction/shock. In addition, the observed patterns of taking lower doses than recommended and early treatment withdrawals due to adverse reactions should be thoroughly evaluated and strategies proposed to limit exposure of patients at high risk for developing serious adverse reactions and to generally increase the tolerance to Mysimba (naltrexone, bupropion).

The PRAC recommendation is without prejudice to the current non-compliance with the condition of the marketing authorisation to conduct and submit results of a study assessing the effect of Mysimba (naltrexone.bupropion) on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects, the uncertainty on the long-term cardiovascular safety profile and how these impact on the benefit-risk balance of Mysimba.

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

6.1.10. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/202209

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

²⁶ Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

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 Keytruda, a centrally authorised medicine containing pembrolizumab 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 Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide cumulative reviews of risk of concomitant use with proton pump inhibitors, of ileus and of thrombotic thrombocytopenic purpura. In addition, the MAH should provide a review of cases of cutaneous vasculitis and discuss the need for an update of the product information as warranted. Finally, the MAH should discuss new information regarding the populations categorised as missing information included in the PSUR list of safety concerns.

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.

In the next regulatory procedure affecting the RMP, the MAH is requested to propose an updated version of the key elements of the patient card (that covers all the relevant and important key elements to mitigate the important identified risk immune-related adverse reactions) and can be used as a single document that replace the current available educational materials; with this, the patient guide will cease to exist.

6.1.11. Ponesimod - PONVORY (CAP) - PSUSA/00010940/202209

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Anette Kirstine Stark

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 Ponvory, a centrally authorised medicine containing ponesimod 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 Ponvory (ponesimod) in the approved indication(s) remains unchanged.

- Nevertheless, the product information should be updated to add seizure as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁷.
- In the next PSUR, the MAH should provide details regarding number of doses missed for cases reporting 'product dose omission issue', as well as all cases of medication errors independently of their seriousness. In addition, the MAH should provide a cumulative review of all cases of skin cancer, including basal cell carcinoma and malignant melanoma, as well as causality assessment and discuss the need for an update of the product information. The MAH should also discuss the need for updating the product information to include a skin examination for all patients at treatment initiation, and then every 6 to 12 months taking into consideration clinical judgement connected to the known cases of cutaneous malignancies. The MAH should also reclassify the risk 'convulsions' from an important potential risk to an important identified in the list of safety concerns and update the RMP accordingly.

The frequency of PSUR submission should be revised from 6-monthly to yearly and the next PSUR should be submitted to EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.12. Pralsetinib - GAVRETO (CAP) - PSUSA/00010961/202209

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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 Gavreto, a centrally authorised medicine containing pralsetinib 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 Gavreto (pralsetinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add tuberculosis as a warning and as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.
- The MAH should submit to EMA, by 19 April 2023, a proposal for a direct health care professional communication (DHPC) and a communication plan aiming at informing

²⁷ 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.

²⁸ Update of SmPC section 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion.

health care professionals about the new risk on tuberculosis as well as the measures to be taken to minimise this risk.

- In the next PSUR, the MAH should discuss the safety signal of peripheral neuropathy.

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.

6.1.13. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/202208

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

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 Zelboraf, a centrally authorised medicine containing vemurafenib 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 Zelboraf (vemurafenib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add thrombocytopenia as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.
- In the next PSUR, the MAH should present a cumulative review of cases of serious haemorrhage, including a comprehensive causality assessment.

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

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

See also Annex I 16.2.

6.2.1. Midazolam^{30 31} - BUCCOLAM (CAP); NAP - PSUSA/00010118/202209

Applicant(s): Laboratorios Lesvi S.L. (BUCCOLAM), various

²⁹ 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.

³⁰ Oromucosal solution

³¹ Indicated for the treatment of prolonged, acute, convulsive seizures

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Midazolam is a benzodiazepine indicated for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years).

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Buccolam, a centrally authorised medicine containing midazolam, and nationally authorised medicines containing midazolam as oromucosal solution indicated for the treatment of prolonged acute convulsive seizures 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 midazolam-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add anaphylactic reaction as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied³².
- In the next PSUR, the MAH of Buccolam (midazolam) should provide a review of cases of Kounis syndrome associated with oromucosal midazolam administration by distinguishing the cases between seizure indication and other indications such as sedation. The MAH should discuss a proposal to update the product information as warranted. Furthermore, the MAH should further discuss cases reporting 'product use issue', as well as the need for reclassification of 'medication error' from important potential risk to important identified risk. The MAH of Buccolam should also provide a review of new cases of choking/asphyxiation on syringe cap and of use in children <6 months of age and discuss relevant safety information from the (ongoing) 'Buccolam Special Drug Use-Results Survey' (if any).

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. Pantoprazole - CONTROLOC CONTROL (CAP); PANTOZOL CONTROL (CAP); SOMAC CONTROL (CAP); NAP - PSUSA/00002285/202208

Applicant(s): Takeda GmbH (CONTROLOC Control, PANTOZOL Control, SOMAC Control), various

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

Background

Pantoprazole is a proton pump inhibitor (PPI), indicated in the treatment of duodenal or gastric ulcer, reflux oesophagitis, Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions and *Helicobacter pylori* eradication, subject to certain conditions.

³² Update of SmPC section XX. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Controloc Control, Pantozol Control and Somac Control, centrally authorised medicines containing pantoprazole, and nationally authorised medicines containing pantoprazole 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 pantoprazole-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH(s) should submit cumulative reviews of cases of drug-induced enterocolitis syndrome (DIES), autoimmune hepatitis, acute kidney injury, chronic kidney disease, end stage renal disease, renal failure, renal injury and rhabdomyolysis. The MAH(s) should also provide cumulative reviews of cases of hypoparathyroidism, gastric neoplasms malignant and of cases of drug-drug interaction (DDI) between pantoprazole and immune checkpoint inhibitors (ICIs) and discuss whether an update of the product information (PI) is warranted. In addition, the MAH(s) should also provide a cumulative review of cases of DDI between levothyroxine-based medicines and pantoprazole and propose an amendment to the PI as per the PRAC recommendation adopted in October 2022³³ for levothyroxine-containing medicinal products (see [PRAC minutes October 2022](#)). Finally, the MAH should continue monitoring cases of acute tubulointerstitial nephritis (TIN) and should provide a cumulative review of the management/actions taken in case of acute TIN while using pantoprazole, as well as discuss an update of the PI as warranted.

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

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

See also Annex I 16.3.

6.3.1. Adenosine (NAP) - PSUSA/00000062/202208

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Adenosine is an antiarrhythmic, indicated for use in conjunction with radionuclide myocardial perfusion imaging in adults who cannot exercise adequately or for whom exercise is inappropriate, for the rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias in adults and children including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome), and as an aid to diagnosis of broad or narrow complex supraventricular tachycardias, subject to certain conditions.

³³ Held on 26-29 September 2022

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing adenosine 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 adenosine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'arteriospasm coronary which may lead to myocardial infarction' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.

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

6.3.2. Midazolam³⁵ (NAP) - PSUSA/00002057/202209

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Midazolam is a benzodiazepine exerting a sedative and sleep-inducing effect of pronounced intensity, as well as an anxiolytic and a muscle-relaxant effect. Midazolam is indicated in adults and children for conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia, anaesthesia and for sedation in intensive care units.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicines containing midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) 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 midazolam-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add Kounis syndrome as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied.
- In the next PSUR, the MAH(s) should further monitor cases of parasomnia associated with midazolam use. Furthermore, the MAH Cheplapharm should provide a cumulative review of cases of tachyarrhythmia, including clinical trial data, literature and post-

³⁴ 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.

³⁵ All pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures

marketing data, as well as a causality assessment and discuss whether an update of the product information (PI) is warranted. In addition, the MAHs Cheplapharm, Sandoz, Hameln Pharma, Sun Pharmaceuticals and Mercury Pharmaceuticals should provide cumulative reviews of cases of Alzheimer's disease and discuss whether updates of the PI are 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

None

6.5. Variation procedure(s) resulting from PSUSA evaluation

See Annex I 16.5.

6.6. Expedited summary safety reviews³⁶

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)³⁷

See also Annex I 17.1.

7.1.1. Fosdenopterin - NULIBRY (CAP) - EMEA/H/C/PSP/S/0103

Applicant: Zydus France S.A.S.

PRAC Rapporteur: Martin Huber

Scope: Submission of a PASS protocol to characterise and assess the long-term safety and efficacy of NULIBRY prescribed in routine practice for patients with molybdenum cofactor deficiency (MoCD) Type A

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.

In order to fulfil the specific obligation to conduct a PASS ([Annex II-E](#)) imposed in the marketing authorisation(s) of Nulibry (fosdenopterin), the MAH Zydus France S.A.S. submitted to EMA a PASS protocol for the study entitled: 'A Non-interventional Post Authorisation Safety Study (PASS) of Patients with MoCD Type A Treated with NULIBRY (fosdenopterin)' for review by PRAC. PRAC is responsible for evaluating the PASS protocol

³⁶ 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

³⁷ In accordance with Article 107n of Directive 2001/83/EC

and any substantial amendments.

Endorsement/Refusal of the protocol

- Having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, PRAC objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that that the design of the study did not fulfil the study objectives at this stage.
- The MAH should provide further clarification on the study milestones, rationale, study design, setting, variables, data sources, as well as on data analysis, quality control, limitations of the research methods, and management and reporting of adverse events/adverse reactions.
- The MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)³⁸

See also Annex I 17.2.

7.2.1. Linzagolix choline - YSELTY (CAP) - EMEA/H/C/005442/MEA 002

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of a protocol for study YSELTY PASS: A multinational PASS on real-world treatment in patients receiving YSELTY (linzagolix choline) for moderate to severe symptoms of uterine fibroids, to evaluate routinely collected data on bone mineral density and to assess safety during long term (>12 months) use for linzagolix 200mg (with ABT) and 100mg (with and without ABT) dosing regimen

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.

As part of the [RMP](#) for Yselty (linzagolix choline), the MAH was required to conduct a PASS in order to address 'bone mineral density decrease with continued linzagolix-treatment > 12 months' as missing information as part of the safety concerns. The MAH submitted a protocol 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 Yselty (linzagolix choline), could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to EMA within 60 days.

³⁸ 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

- PRAC considered that the proposed primary objective is not in line with the objective defined in the RMP and does not address the missing information 'bone mineral density decrease with continued linzagolix-treatment > 12 months'. The MAH should provide further clarification on the new proposed study design, as well as to consider whether the risk of bones and fractures could be addressed in an exploratory objective. The MAH should update the study milestones, duration, data analysis and other sections in order to adequately reflect any revision for the primary objective.

7.2.2. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004893/MEA 002.2

Applicant: TMC Pharma (EU) Limited

PRAC Rapporteur: Julia Pallos

Scope: Submission of a revised protocol (version no.3.0) 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

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.

As part of the [RMP](#) for Sunosi (solriamfetol), the MAH was required to conduct a PASS in order to evaluate the long term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol. The MAH submitted a protocol for a study for evaluation which was assessed by the Rapporteur. PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH. For further background, see [PRAC minutes December 2020](#).

Summary of advice

- The study protocol for Sunosi (solriamfetol) could be acceptable provided an updated protocol and satisfactory responses to a request for supplementary information (RSI) is submitted to EMA by 31 May 2023.
- PRAC considered that the MAH should provide further clarification on the study objectives, feasibility, as well as on data sources.

7.3. Results of PASS imposed in the marketing authorisation(s)³⁹

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁰

See also Annex I 17.4.

7.4.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0092

Applicant: Genzyme Europe BV

³⁹ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁰ 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

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy, lactation and fertility following the request by PRAC in the AR for MEA/024.17 and MEA/025.17 and in the PSUR single assessment (PSUSA) procedure (PSUSA/00000086/202109) concluded in June 2022. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

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.

As stated in the RMP of Myozyme, the MAH conducted a non-imposed non-interventional PASS Pompe Safety Sub-Registry - AGLU06909/LTS13930. 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 December 2022](#).

Summary of advice

- Based on the available data, the MAH's responses to the RSI and the Rapporteur's review, PRAC considered that the ongoing variation assessing the final study report could be recommended for approval.

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. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 011.8

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.6 [Interim report for study C4591010: a post-approval active surveillance safety study to monitor real-world safety of Comirnaty (tozinameran) vaccine in the EU] as per request for supplementary information (RSI) adopted in December 2022

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.

As part of the [RMP](#) for Comirnaty (tozinameran), the MAH had committed to perform a study to estimate the incidence rates of medically attended safety events of interest [based on the list of adverse events of special interest (AESI)] and other clinically significant events among persons vaccinated with the COVID-19 mRNA vaccine and to assess whether these rates elevated relative to estimated expected rates. The interim results were assessed by the Rapporteur for PRAC review.

Summary of advice

- PRAC noted that during the COVID-19 pandemic, safety data for Comirnaty (tozinameran) has been gathered from other sources and the knowledge of the safety profile of Comirnaty has increased over time. Consequently, taking also into account recruitment challenges for this study design in the COVID-19 pandemic, the value of the results of study C4591010 with the number of included participants being lower than specified in the protocol has decreased. PRAC considered that the study results are unlikely to contribute to a meaningful further characterisation of the safety profile of Comirnaty beyond the results from ongoing database studies C4591021 and C4591052, and other pharmacovigilance activities. Therefore, PRAC considered that the study C4591010 (listed as category 3 study) should be removed from the RMP.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

None.

7.8. Ongoing Scientific Advice

None.

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

None.

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

8.1. Annual reassessments of the marketing authorisation

See also Annex I 18.1.

8.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0045 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

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.

Scenesse, a centrally authorised product containing afamelanotide, was authorised in 2014 under exceptional circumstances. The benefit-risk of Scenesse is reviewed on a yearly basis by CHMP based on the submission and assessment of additional post-authorisation data (i.e.

specific obligations). PRAC is responsible for providing advice to CHMP on this annual re-assessment with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available information on the status of the fulfilment of specific obligations and safety data submitted, PRAC considered that the annual re-assessment procedure for Scenesse could be finalised if the MAH provides satisfactory responses to a request for supplementary information (RSI). PRAC noted that, according to the [Annex II-D](#), the MAH did not fulfil the obligation to submit final study report for the Retrospective Chart Review (RCR) study 6 years after approval, thus in 2020. The MAH should provide further clarification regarding the feasibility of the study, as well as whether the study is intended to be continued, and postpone the submission of the final report. If this is the case, the MAH should duly justify the modification proposal in a separate regulatory procedure.

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

The PRAC Chair welcomed Eamon O Murchu as the new alternate for Ireland (mandate started on 24 March 2023).

12.1.2. Vote by proxy

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. Coronavirus (COVID-19) pandemic - update

The EMA Secretariat updated PRAC on the activities of the COVID-19 EMA pandemic Task Force (ETF), including an overview of the ongoing clinical trials to evaluate the safety and efficacy of medicines in development as potential treatments for COVID-19, as well as study

results on effectiveness of COVID-19 mRNA vaccines' (booster dose and adapted mRNA bivalent vaccines) against the new Omicron subvariants. The EMA Secretariat also updated PRAC on prevalence and characteristics of the post-COVID-19 condition observed in both adult and paediatric populations, as well as on cases of influenza A virus H5N1 worldwide and Marburg virus outbreaks in Africa.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. Marketing authorisation applications (MAA) forecast for 2023 – planning update dated Q1 2023

At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 April 2023, the EMA Secretariat presented for information to PRAC a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline') in 2023. For previous update, see [PRAC minutes January 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

In line with the criteria for plenary presentation of updates to the EURD List adopted by PRAC in December 2021, PRAC endorsed the draft revised EURD list, version April 2023, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

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

12.11. Signal management

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

PRAC lead: Menno van der Elst

PRAC was updated on the progress from the SMART working group meeting on Methods held on 6 March 2023, including the group's workplan for 2023, as well as further information about lessons learned on observed versus-expected (O/E) analyses to support COVID-19 vaccine safety monitoring and from experimenting with health data.

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) - publication on EMA website

At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 April 2023, the EMA Secretariat presented to PRAC an update on the EMA initiative to publish RMPs⁴¹ of centrally authorised products (together with all subsequent updates) in order to further increase the transparency of safety information to the public and stakeholders. For further background, see [PRAC minutes May 2022](#). The EMA Secretariat presented to PRAC the proposal of having the initiative extended to all RMPs (together with all subsequent updates) included in the initial marketing authorisation applications and post-authorisation procedures, which were submitted with procedures starting on or after 1 June 2023. PRAC members were invited to send any comments on the proposal.

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

⁴¹ In replacement of the RMP summaries

12.16.2. Lessons learned on referral procedures – case study

Following the finalisation of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on Janus kinase inhibitors (JAKis) in early 2023, the EMA Secretariat presented to PRAC an overview of the procedure, together with the key successes and lessons learnt from the management of this class review. PRAC noted this information and points useful for future procedures.

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. Study on the impact of EU label changes for fluoroquinolone-containing medicinal products for systemic and inhalation use: post-referral prescribing trends - follow-up discussion on PRAC Sponsors' assessment

PRAC lead: Eva Jirsová, Martin Huber

PRAC concluded the discussion on the results of the study on "Impact of European Union Label Changes for Fluoroquinolone Containing Medicinal Products for Systemic and Inhalation Use" (EUPAS37856) following the PRAC Sponsors' updated assessment and comments from Member States. PRAC continued the discussion on elements of a communication strategy, including a direct healthcare professional communication (DHPC) and communication plan, to remind healthcare professionals of the restrictions of use of systemic and inhaled fluoroquinolone antibiotics implemented as part of the outcome of the referral procedure under Article 31 of Directive 2001/83/EC finalised in 2018. For further background, see [PRAC minutes January 2023](#), [PRAC minutes February 2023](#).

12.21. Others

12.21.1. EMA expert management systems update on the new Experts Management Tool

The EMA Secretariat presented to PRAC the new EMA Expert Management tool: a platform

where EMA maintains a list of all medicine and medical device experts involved in medicines and medical devices-related activities, as well as the members of the EMA Management Board (MB), together with their declarations of interests (DoIs) and CVs. PRAC noted the information.

12.21.2. PRAC drafting group on the risks of dependence and addiction of opioids - update

Following the PRAC plenary meeting in November 2022⁴², PRAC agreed on the need for increasing the awareness on the serious risk of opioid use disorder (OUD) for medicinal products containing opioids for prescribers and patients in order to protect public health. A drafting group was established to develop a proposal for PRAC's consideration, having its first meeting on 16 December 2022, where it agreed on the distribution of a non-urgent information (NUI) collecting the perspectives of all EU Member States on a potential warning on the outer packaging for relevant opioids. At their second meeting held on 21 March 2023, the group reviewed the NUI responses and agreed on the next steps.

At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 April 2023, PRAC was informed on the interim report of the PRAC drafting group of the risks of dependence and addiction on opioids and agreed on the next steps. PRAC supported the need for a stakeholder consultation in this respect. PRAC members were invited to send comments on the questions for the stakeholder survey.

12.21.3. EMA policy on handling of competing interests for scientific committees' members and experts – revision of policy 0044

The EMA Secretariat informed PRAC on the update of the EMA Policy on the handling of competing interests of scientific committees' members and experts ([policy 0044](#)) due to the implementation of the new Medical Device and *in vitro* Medical Device Regulations (Regulations (EU) 2017/745 and 2017/746), as well as of EMA's Extended Mandate Regulation (Regulation (EU) 2022/123) where EMA will have new tasks in the area of medical devices. The EMA Secretariat explained the main changes as well as the responsibilities and obligations of experts regarding their declarations of interests. The updated policy became effective as of 1 January 2023. PRAC noted the information.

12.21.4. EMA Stakeholder meeting - European Federation of Pharmaceutical Industries and Associations (EFPIA) study report on 'Industry perspective on post-authorisation safety study (PASS)' (2016-2022)

PRAC lead: Sabine Straus, Martin Huber

At the organisational, regulatory and methodological matters (ORGAM) meeting on 26 April 2023, PRAC was informed about the results of the questionnaire that was launched following the EMA Stakeholder meeting held on 17 November 2021, where one of the aims was to better understand the industry's perspective on the current process of initiating and conducting a PASS. In order to collect feedback from a broad range of pharmaceutical companies concerning their experience with PASS listed in the RMP (committed to or requested by EMA or EU Regulatory Authorities) and the related processes and interactions with European Regulatory Authorities, the Pharmacovigilance Expert Group of EFPIA (PVEG) together with the Pharmacovigilance Committee of Medicines for Europe (MfE), developed a

⁴² Held on 24-27 October 2022

questionnaire in this respect. The results of the EFPIA's study report were discussed by PRAC. PRAC acknowledged the study report highlighting that the feasibility assessments for PASSes are now requested regularly by PRAC to evaluate for example the sample size, access and adequacy of the proposed databases and that the advice given for category 3 studies should generally be more high level leaving more flexibility to the MAHs to adapt the protocol to real clinical practice and settings in different Member States. The document will be further discussed in the context of the ongoing revision of the GVP module VIII on 'Post-authorisation safety studies'.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁴³

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 timetables⁴⁴.

14.1. New signals detected from EU spontaneous reporting systems

14.1.1. Acetazolamide (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of choroidal effusion and choroidal detachment

14.1.2. Apalutamide – ERLEADA (CAP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Signal of interstitial lung disease (ILD)

14.1.3. Megestrol (NAP)

Applicant(s): various

PRAC Rapporteur: Eamon O'Murchu

Scope: Signal of meningioma

⁴³ 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

⁴⁴ Either MAH(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.4. Pramipexole⁴⁵ – MIRAPEXIN (CAP); OPRYMEA (CAP); PRAMIPEXOLE TEVA (CAP); SIFROL (CAP); (NAP)

Applicant(s): Boehringer Ingelheim International GmbH (Mirapexin, Sifrol), KRKA, d.d., Novo mesto (Oprymeia), Teva B.V. (Pramipexole Teva), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of intestinal obstruction

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

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

15.1.1. Degarelix acetate - EMEA/H/C/006048

Scope: Treatment of prostate cancer

15.1.2. Pegfilgrastim - EMEA/H/C/005587

Scope: Treatment of neutropenia

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. Efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/II/0130

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP version 9.0 including removal of all safety concerns in line with revision 2 of GVP module V on 'Risk management systems'

15.2.2. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0017, Orphan

Applicant: Zogenix ROI Limited

⁴⁵ Prolonged release tablets

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

15.2.3. Palivizumab - SYNAGIS (CAP) - EMEA/H/C/000257/II/0131

Applicant: AstraZeneca AB

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Submission of an updated RMP version 2.0 in order to remove from the list of safety concerns "Anaphylaxis, Anaphylactic shock, and Hypersensitivity" and "Medication error of mixing lyophilised and liquid palivizumab before injection". In addition, the MAH took the opportunity to apply the revised template

15.2.4. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000315/II/0077

Applicant: Ipsen Pharma

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP version 4.0 in order to remove some of the safety concerns in compliance with GVP Module V Revision 2. In addition, the MAH took the opportunity to add data from final clinical study report of International Cooperative Growth Study (iNCGS) registry (non-interventional study) and exposure and safety information

15.2.5. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS2402/0069; MODIGRAF (CAP) - EMEA/H/C/000954/WS2402/0045

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eamon O'Murchu

Scope: Submission of an updated RMP (version 4) to reflect the new Transplant Pregnancy Registry International (TPRI) final study submission milestone, related to procedure EMEA/H/C/000712/MEA030 and EMEA/H/C/000954/MEA022 (Study F506-PV-0001), from 21 December 2021 to 30 June 2023

15.2.6. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0059

Applicant: Amgen Europe B.V., ATMP⁴⁶

PRAC Rapporteur: Gabriele Maurer

Scope: Submission of an updated RMP version 10 in order to update and reclassify identified risk of 'disseminated herpetic infection' based on the cumulative assessment of literature review and MAH Global Safety Database and to remove studies 20180062 and 20180099 from Planned and Ongoing Studies from the list of Pharmacovigilance Plan studies in the Annex II

⁴⁶ Advanced therapy medicinal product

15.2.7. 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

15.2.8. Tobramycin - TOBI PODHALER (CAP) - EMEA/H/C/002155/II/0053, Orphan

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of an updated RMP version 8.0 following PSUR single assessment (PSUSA) procedure (PSUSA/00009315/202106) concluded in February 2022 in order to update it based on the guidance provided in the GVP and to remove the safety concerns as well as to reflect the finalisation of study CTBM100C2407 and the transfer of ownership

15.2.9. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/II/0061

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP version 12 in order to remove certain risks from the list of safety concerns

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. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0094

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Update of section 4.2 of the SmPC in order to add home infusion upon request by PRAC following the assessment of PSUSA/00000086/202109 based on a cumulative search of the MAH Global Pharmacovigilance database and literature. The package leaflet and Annex II are updated accordingly. The RMP version 10.0 has also been submitted

15.3.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0095

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Update of sections 4.4 and 5.2 of the SmPC in order to update warning on immunogenicity. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information

15.3.3. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0077/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: Grouped application comprising two type II variations as follows: 1) Update of sections 4.2, 4.4. and 4.8 of the SmPC in order to add dose modification advice and new warning for two new important identified risks of immune-mediated myelitis and immune-mediated facial paresis and to add facial paresis and myelitis to the list of adverse drug reactions (ADRs) with frequency Rare following a safety signal based on the cumulative review of the MAH safety database and literature search; 2) Update of section 4.8 of the SmPC in order to add dry mouth to the list of adverse drug reactions (ADRs) with frequency Common, based on the results from study WO39210 (IMmotion010), a multicenter, randomised, placebo-controlled, double-blind study evaluating the efficacy and safety of atezolizumab versus placebo in patients with renal cell carcinoma (RCC) who are at high risk of disease recurrence following resection.

The Annex II and package leaflet are updated accordingly. The RMP version 26.0 has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the SmPC and to update the list of local representatives in the package leaflet

15.3.4. Avapritinib - AYVAKYT (CAP) - EMEA/H/C/005208/II/0022, Orphan

Applicant: Blueprint Medicines (Netherlands) B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations and to update pharmacokinetic information for use in patients with severe hepatic impairment based on the final results from study BLU-285-0107 listed as a category 3 study in the RMP; this is a phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of avapritinib. The package leaflet is updated accordingly. The RMP version 3.0 has also been submitted. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version 10.3

15.3.5. 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

15.3.6. Azacitidine - AZACITIDINE ACCORD (CAP) - EMEA/H/C/005147/X/0013

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (10 mg/ml powder for solution for infusion) and a new route of administration (intravenous use). The RMP version 2 is updated in accordance

15.3.7. Casirivimab, imdevimab - RONAPREVE (CAP) - EMEA/H/C/005814/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of coronavirus (COVID-19) in hospitalised patients in adults and adolescents aged 12 years and older weighing at least 40 kg. As a consequence, sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet, the labelling and the RMP (version 1.1) are updated in accordance

15.3.8. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS2421/0059; FORXIGA (CAP) - EMEA/H/C/002322/WS2421/0080

Applicant: AstraZeneca AB

PRAC Rapporteur: Mari Thorn

Scope: Submission of final results from non-clinical mechanistic model studies listed as a category 3 PASS in the RMP. These are non-clinical studies aiming to further investigate underlying mechanisms of diabetes ketoacidosis (DKA) in association with dapagliflozin. The RMP version 29 has also been submitted

15.3.9. Ebola Zaire vaccine (live, attenuated) - ERVEBO (CAP) - EMEA/H/C/004554/II/0025

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include the paediatric population from 1 year to less than 18 years of age based on final results from study V920-016 (PREVAC); this is a phase 2, randomised, double-blind, placebo-controlled study of 2 leading Ebola vaccine candidates (Ad26.ZEBOV/MVA-BN-Filo and V920) and 3 vaccine strategies (Ad26.ZEBOV/MVABN-Filo, 1-dose V920, and 2 dose V920) to evaluate immunogenicity and safety in healthy children and adolescents from 1 to 17 years of age and adults 18 years of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.3 of the SmPC are updated. The package leaflet is updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the Annex II and the list of local representatives in the package leaflet

15.3.10. [Elasomeran - SPIKEVAX \(CAP\) - EMEA/H/C/005791/II/0097/G](#)

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variation consisting of : 1) Extension of indication to include a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran) in children aged 6 through 11 years of age; as a consequence, sections 2, 4.1, 4.2, 4.4, and 6.6 of the SmPC are updated. The package leaflet and Labelling are updated in accordance. Version 6.5 of the RMP has also been submitted; 2) Update of sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.1 SmPC to add median follow-up period and D91 persistence data, based on Parts F and G (mRNA- 1273.214) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines. The package leaflet is updated accordingly; 3) Update sections 4.8 and 5.1 of the Spikevax bivalent Original/Omicron BA.4-5 SmPC to add ADR details and clinical data, based on Part H (mRNA- 1273.222) of study mRNA-1273-P205 (NCT04927065), an open-label Phase 2/3 study evaluating the immunogenicity and safety of variant-targeting booster candidate vaccines. In addition, the Marketing authorisation holder took the opportunity to implement a number of editorial changes to the product information

15.3.11. [Empagliflozin - JARDIANCE \(CAP\) - EMEA/H/C/002677/II/0076](#)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Extension of indication for JARDIANCE to include treatment of children aged 10 years and above with type 2 diabetes based on results from study DINAMO 1218-0091; this is a double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 21.0 of the RMP has also been submitted

15.3.12. [Follitropin delta - REKOVELLE \(CAP\) - EMEA/H/C/003994/II/0037/G](#)

Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Grouped application consisting of: 1) Update of sections 4.1, 4.2, 4.4, 4.5 and 5.1 of the SmPC to update the safety information following final results from study 000304 (BEYOND). This is a randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 (follitropin delta) dosing, using a long gonadotropin-releasing hormone (GnRH) agonist protocol and a GnRH antagonist protocol in women undergoing controlled ovarian stimulation; 2) Update of section 4.8 of the SmPC, including the tabulation of adverse drug reactions based on pooled safety data from studies ESTHER-1, ESTHER-2, 000273, 000145, BEYOND and RAINBOW. The updated RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.13. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0011/G, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Grouped application consisting of: 1) update of section 5.3 of the SmPC based on final results from study AS1-GLP18-007 listed as a category 3 study in the RMP: a 104-week subcutaneous injection carcinogenicity study in Sprague Dawley rats; 2) update of section 5.3 of the SmPC based on final results from study AS1-GLP18-004: a 26-week subcutaneous injection carcinogenicity study in TgRasH2 mice. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.14. Hydroxycarbamide - XROMI (CAP) - EMEA/H/C/004837/II/0019

Applicant: Nova Laboratories Ireland Limited

PRAC Rapporteur: Jo Robays

Scope: Extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 6 months to 2 years of age for Xromi, based on final results from the paediatric study INV543, listed as a category 3 study in the RMP; this is a single-arm, open-label, multi-center study in children with sickle cell anaemia over 6 months of age. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted

15.3.15. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0100

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include in combination with nivolumab the treatment of adolescents (12 years of age and older) for advanced (unresectable or metastatic) melanoma, based on the pivotal study CA209070; this is a multicentre, open-label, single arm, phase 1/2 trial of nivolumab +/- ipilimumab in children, adolescents and young adults with recurrent or refractory solid tumours or lymphomas. 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 38.0 of the RMP has also been submitted

15.3.16. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0114/G

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Monica Martinez Redondo

Scope: Extension application to add a new strength (59.5 mg) of the granules pharmaceutical form grouped with a type II variation to support a new indication in a combination regimen with ivacaftor/tezacaftor/elexacaftor 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 RMP (version 15.1) has also been submitted. Type IB B.II.f.1.b - to

extend the shelf-life of the granules pharmaceutical form of the finished product as packaged for sale from 3 to 4 years. The product information has been updated accordingly

15.3.17. 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

15.3.18. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones. The updated RMP version 38 was provided

15.3.19. Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/II/0052

Applicant: Eisai GmbH

PRAC Rapporteur: David Olsen

Scope: Update of section 4.8 of the SmPC based on pooled safety data including results of Study 307, an ongoing, multicentre, randomised, open-label study that is being conducted to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line (1L) treatment in adults with advanced renal cell carcinoma (RCC). The provision of the clinical study report (CSR) addresses the post-authorisation measure MEA/FSR 009.3. The package leaflet is updated accordingly. An updated RMP version 15.0 has been submitted

15.3.20. Lumacaftor, ivacaftor - ORKAMBI (CAP) - EMEA/H/C/003954/X/0078/G

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped application consisting of: 1) Extension application to add a new strength of 75 mg of lumacaftor and 94 mg of ivacaftor fixed dose combination granules; 2) Extension of indication to include treatment of cystic fibrosis for children aged 1 to less than 2 years old of age who are homozygous for the F508del mutation in the CFTR gene, based on final results from study 122, a 2-part study of cystic fibrosis (CF) subjects 1 to <2 years of age homozygous for F508del. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 11.2 of the RMP has also been submitted

15.3.21. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0039

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC in order to update information regarding the use of naloxegol in opioid-induced constipation (OIC) patients with cancer-related pain based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature. The package leaflet is updated accordingly. The RMP version 8 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC

15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0125/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo, based on results from a nonclinical biomarker study (Expression of PD-L1 (CD274), and characterization of tumour infiltrating immune cells in tumours of paediatric origin), also based on results from a Phase 1/2 clinical study (CA209070, a phase 1/2 study of Nivolumab (Ind# 124729) in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with Ipilimumab) and a modelling and simulation study. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet is updated in accordance. Version 30.0 of the RMP has also been submitted

15.3.23. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Monica Martinez Redondo

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the

tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the pregnancy prevention plan (PPP) will not be impacted. The updated RMP version 16 was provided

15.3.24. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0064, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include treatment of newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), either with Iclusig (ponatinib) in combination with chemotherapy, or with Iclusig (ponatinib) monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens, based on final results from studies AP24534-11-001 and INCB 84344-201. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 22 of the RMP has also been submitted

15.3.25. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0037

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years of age with WHO Functional Class (FC) I to III in combination with endothelin receptor antagonists with or without prostanoids for Adempas (riociguat), based on results from pivotal study PATENT-CHILD (Study 15681); this is a Phase III, Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with PAH; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the package leaflet

15.3.26. Siponimod - MAYZENT (CAP) - EMEA/H/C/004712/II/0020

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add "Progressive multifocal leukoencephalopathy (PML)" to the list of adverse drug reactions (ADRs) with frequency "not know" based on post-marketing data. The Annex II (Physician's Checklist), and package leaflet are updated accordingly. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to update the text regarding herpes viral infection in the package leaflet in alignment with the currently approved SmPC

15.3.27. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/II/0054/G, Orphan

Applicant: Takeda Pharmaceuticals International AG Ireland Branch

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Grouped variations consisting of: 1) extension of indication to include patients from 4 months corrected gestational aged 1 year and above. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 9.1) are updated accordingly; 2) update of Annex II-D on 'Conditions or restrictions with regards to the safe and effective use of the medicinal product' to amend the date of completion of the imposed post authorisation study: an international short bowel syndrome registry, from Q3 2031 to Q2 2032. In addition, the MAH took the opportunity to amend the list of local representatives

15.3.28. Teriflunomide - AUBAGIO (CAP) - EMEA/H/C/002514/II/0042

Applicant: Sanofi Winthrop Industrie

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study EFC11759 listed as a category 3 study in the RMP. This is a two-year, multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide administered orally once daily in paediatric patients with relapsing forms of multiple sclerosis (MS) followed by an open-label extension. The RMP version 8.0 has also been submitted

15.3.29. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Update of section 4.4 of the SmPC, Annex IID and Article 127a and the tools/documents included in the Educational Healthcare Professional Kit, in order to harmonise the terminology utilised in the RMP and product information documents relating to the safety concern of teratogenicity and its risk minimisation measure of the Pregnancy Prevention Plan (PPP) across the 3 immunomodulatory imide drugs (IMiDs). These proposed changes will only have a limited impact on the National Competent Authority (NCA)-approved content/text of the educational materials, and the key messages to the HCP and patients. Furthermore, the regulatory obligations regarding the PPP will not be impacted. The MAH is also taking the opportunity to update the RMP with PASS Protocol milestones, and to make some editorial changes in the labelling. The updated RMP version 20 was provided

15.3.30. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0114

Applicant: Roche Registration GmbH

PRAC Rapporteur: Gabriele Maurer

Scope: Extension of indication to include treatment of new indication for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial

lung disease (SSc-ILD) for RoActemra, based on final results from the pivotal Phase III Study WA29767 (focuSSced) entitled, "A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis" and the supportive Phase II/III Study WA27788 (faSScinate) entitled, "A Phase II/III, Multicenter, Randomised, Double-blind, Placebo-controlled Study To Assess The Efficacy And Safety Of Tocilizumab Versus Placebo In Patients With Systemic Sclerosis". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. Version 28 of the RMP has also been submitted

15.3.31. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0096

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Update of section 5.1 of the SmPC in order to update information with the 4-year clinical data in patients with ulcerative colitis based on the final report from study CNT01275UCO3001 listed as a category 3 study in the RMP; this is a phase 3, randomised, double blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. The RMP version 23.1 has also been submitted. In addition, the MAH took the opportunity to introduce a correction to the product information

15.3.32. Zanubrutinib - BRUKINSA (CAP) - EMEA/H/C/004978/II/0009

Applicant: BeiGene Ireland Ltd

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study BGB-3111-113 - A Drug-Drug Interaction Study of Zanubrutinib with Moderate and Strong CYP3A Inhibitors in Patients With B-Cell Malignancies, listed as a category 3 study in the RMP. The RMP version 3.0 has also been submitted

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

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

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

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

16.1.1. Abrocitinib - CIBINQO (CAP) - PSUSA/00010976/202209

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Nikica Mirošević Skvrce
Scope: Evaluation of a PSUSA procedure

16.1.2. Avacopan - TAVNEOS (CAP) - PSUSA/00010967/202209

Applicant: Vifor Fresenius Medical Care Renal Pharma France
PRAC Rapporteur: Liana Gross-Martirosyan
Scope: Evaluation of a PSUSA procedure

16.1.3. Bedaquiline - SIRTURO (CAP) - PSUSA/00010074/202209

Applicant: Janssen-Cilag International N.V.
PRAC Rapporteur: Ulla Wändel Liminga
Scope: Evaluation of a PSUSA procedure

16.1.4. Cenobamate - ONTOZRY (CAP) - PSUSA/00010921/202209

Applicant: Angelini S.p.A.
PRAC Rapporteur: Jo Robays
Scope: Evaluation of a PSUSA procedure

16.1.5. Cholic acid⁴⁷ - ORPHACOL (CAP) - PSUSA/00010208/202209

Applicant: Laboratoires CTRS
PRAC Rapporteur: Sofia Trantza
Scope: Evaluation of a PSUSA procedure

16.1.6. Copper (64Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/202208

Applicant: A.C.O.M. - Advanced Center Oncology Macerata - S.R.L.
PRAC Rapporteur: Amelia Cupelli
Scope: Evaluation of a PSUSA procedure

16.1.7. Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/202208

Applicant: Novartis Europharm Limited
PRAC Rapporteur: Ulla Wändel Liminga

⁴⁷ Oxosteroid-reductase or hydroxy-steroid dehydrogenase deficiency indication(s) only

Scope: Evaluation of a PSUSA procedure

16.1.8. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202209

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.9. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202209

Applicant: Takeda Pharma A/S, ATMP⁴⁸

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.10. Duvelisib - COPIKTRA (CAP) - PSUSA/00010939/202209

Applicant: Secura Bio Limited

PRAC Rapporteur: Željana Margan Koletić

Scope: Evaluation of a PSUSA procedure

16.1.11. Ebola vaccine (rDNA⁴⁹, replication-incompetent) - MVABEA (CAP); ZABDENO (CAP) - PSUSA/00010857/202209

Applicant(s): Janssen-Cilag International N.V.

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.12. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/202208

Applicant: Genzyme Europe BV

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.13. Filgotinib - JYSELECA (CAP) - PSUSA/00010879/202209

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

16.1.14. Fremanezumab - AJOVY (CAP) - PSUSA/00010758/202209

Applicant: TEVA GmbH

⁴⁸ Advanced therapy medicinal product

⁴⁹ Recombinant deoxyribonucleic acid

PRAC Rapporteur: Kirsti Villikka
Scope: Evaluation of a PSUSA procedure

16.1.15. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202209

Applicant: Eli Lilly Nederland B.V.
PRAC Rapporteur: Kirsti Villikka
Scope: Evaluation of a PSUSA procedure

16.1.16. Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202209

Applicant: Astellas Pharma Europe B.V.
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.17. Human alfa1-proteinase inhibitor⁵⁰ - RESPREEZA (CAP) - PSUSA/00010410/202208

Applicant: CSL Behring GmbH
PRAC Rapporteur: Monica Martinez Redondo
Scope: Evaluation of a PSUSA procedure

16.1.18. Idebenone⁵¹ - RAXONE (CAP) - PSUSA/00010412/202209

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH
PRAC Rapporteur: Amelia Cupelli
Scope: Evaluation of a PSUSA procedure

16.1.19. Insulin aspart - FIASP (CAP); INSULIN ASPART SANOFI (CAP); KIRSTY (CAP); NOVOMIX (CAP); NOVORAPID (CAP); TRUVELOG MIX 30 (CAP) - PSUSA/00001749/202209

Applicant(s): Sanofi Winthrop Industrie (Insulin aspart Sanofi, Truvelog Mix 30), Mylan IRE Healthcare Limited (Kirsty), Novo Nordisk A/S (Fiasp, NovoMix, NovoRapid)
PRAC Rapporteur: Mari Thorn
Scope: Evaluation of a PSUSA procedure

16.1.20. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202209

Applicant: Pfizer Europe MA EEIG
PRAC Rapporteur: Nikica Mirošević Skvrce
Scope: Evaluation of a PSUSA procedure

⁵⁰ Centrally authorised product(s) only

⁵¹ Centrally authorised product(s) only

16.1.21. Lusutrombopag - MULTPLEO (CAP) - PSUSA/00010755/202209

Applicant: Shionogi B.V.

PRAC Rapporteur: Mari Thorn

Scope: Evaluation of a PSUSA procedure

16.1.22. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/202209

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.1.23. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/202209

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.24. Ofatumumab - KESIMPTA (CAP) - PSUSA/00010927/202209

Applicant: Novartis Ireland Limited

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.25. Olipudase alfa - XENPOZYME (CAP) - PSUSA/00011003/202209

Applicant: Genzyme Europe BV

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.26. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202209

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

16.1.27. Pitolisant - OZAWADE (CAP); WAKIX (CAP) - PSUSA/00010490/202209

Applicant(s): Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.28. Raltegravir - ISENTRESS (CAP) - PSUSA/00010373/202209

Applicant: Merck Sharp & Dohme B.V.
PRAC Rapporteur: Nathalie Gault
Scope: Evaluation of a PSUSA procedure

16.1.29. Rilpivirine⁵² - REKAMBYS (CAP) - PSUSA/00010901/202209

Applicant: Janssen-Cilag International N.V.
PRAC Rapporteur: Liana Gross-Martirosyan
Scope: Evaluation of a PSUSA procedure

16.1.30. Ritonavir - NORVIR (CAP) - PSUSA/00002651/202208

Applicant: AbbVie Deutschland GmbH & Co. KG
PRAC Rapporteur: Liana Gross-Martirosyan
Scope: Evaluation of a PSUSA procedure

16.1.31. Selinexor - NEXPOVIO (CAP) - PSUSA/00010926/202209

Applicant: Stemline Therapeutics B.V.
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.32. Tebentafusp - KIMMTRAK (CAP) - PSUSA/00010991/202209

Applicant: Immunocore Ireland Limited
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

16.1.33. Tenecteplase - METALYSE (CAP) - PSUSA/00002888/202208

Applicant: Boehringer Ingelheim International GmbH
PRAC Rapporteur: Martin Huber
Scope: Evaluation of a PSUSA procedure

16.1.34. Tepotinib - TEPMETKO (CAP) - PSUSA/00010979/202209

Applicant: Merck Europe B.V.
PRAC Rapporteur: Menno van der Elst
Scope: Evaluation of a PSUSA procedure

⁵² Intramuscular use only

16.1.35. Tildrakizumab - ILUMETRI (CAP) - PSUSA/00010720/202209

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.36. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/202209

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.1.37. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202209

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.38. Vernakalant hydrochloride - BRINAVESS (CAP) - PSUSA/00003109/202208

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Budesonide, formoterol - BIRESP SPIROMAX (CAP); BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP); DUORESP SPIROMAX (CAP); NAP - PSUSA/00010585/202208

Applicant(s): Teva Pharma B.V. (BiResp Spiromax, Budesonide/Formoterol Teva Pharma B.V., DuoResp Spiromax), various

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.2.2. Glycopyrronium53 - SIALANAR (CAP); NAP - PSUSA/00010529/202209

Applicant(s): Proveca Pharma Limited (Sialanar), various

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

⁵³ Treatment of severe sialorrhoea (chronic pathological drooling) indication(s) only

16.2.3. [Octocog alfa - ADVATE \(CAP\); KOGENATE BAYER \(CAP\); KOVALTRY \(CAP\); NAP - PSUSA/00002200/202208](#)

Applicant(s): Takeda Manufacturing Austria AG (Advate), Bayer AG (KOGENATE Bayer, Kovaltry), various

PRAC Rapporteur: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

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

16.3.1. [Allergen for therapy: dermatophagoides pteronyssinus, dermatophagoides farina54 \(NAP\) - PSUSA/00010582/202209](#)

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.2. [Biperiden \(NAP\) - PSUSA/00000415/202208](#)

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.3. [Choline alfoscerate \(NAP\) - PSUSA/00010599/202208](#)

Applicant(s): various

PRAC Lead: Rugilė Pilvinienė

Scope: Evaluation of a PSUSA procedure

16.3.4. [Dexamfetamine \(NAP\) - PSUSA/00000986/202209](#)

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. [Dornase alpha \(NAP\) - PSUSA/00001164/202209](#)

Applicant(s): various

PRAC Lead: Jana Lukačičinová

Scope: Evaluation of a PSUSA procedure

⁵⁴ Oromucosal use, products authorised via mutually recognition procedure and decentralised procedure

16.3.6. Drospirenone, ethinylestradiol (NAP) - PSUSA/00010217/202209

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.7. Fluoxetine (NAP) - PSUSA/00001442/202209

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.8. Fluvastatin (NAP) - PSUSA/00001457/202208

Applicant(s): various

PRAC Lead: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.3.9. Human tetanus immunoglobulin (NAP) - PSUSA/00002909/202208

Applicant(s): various

PRAC Lead: Gabriele Maurer

Scope: Evaluation of a PSUSA procedure

16.3.10. Minocycline (NAP) - PSUSA/00002065/202208

Applicant(s): various

PRAC Lead: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.3.11. Paricalcitol (NAP) - PSUSA/00002316/202208

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.12. Piperacillin, tazobactam (NAP) - PSUSA/00002425/202209

Applicant(s): various

PRAC Lead: Anna Mareková

Scope: Evaluation of a PSUSA procedure

16.3.13. Tretinoin⁵⁵ (NAP) - PSUSA/00003016/202208

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.3.14. Treosulfan⁵⁶ (NAP) - PSUSA/00009319/202208

Applicant(s): various

PRAC Lead: Marie Louise Schougaard Christiansen

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

16.5. Variation procedure(s) resulting from PSUSA evaluation

16.5.1. Fondaparinux sodium - ARIXTRA (CAP) - EMEA/H/C/000403/II/0087

Applicant: Mylan Ire Healthcare Limited

PRAC Rapporteur: Mari Thorn

Scope: To update section 4.8 of the SmPC to update the ADR table following the assessment of PSUSA (EMEA/H/C/PSUSA/00001467/202112). The package leaflet is updated accordingly

16.6. Expedited summary safety reviews⁵⁷

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)⁵⁸

17.1.1. Evinacumab - EVKEEZA (CAP) - EMEA/H/C/PSA/S/0098.1

Applicant: Regeneron Ireland DAC

⁵⁵ Topical formulation(s) only

⁵⁶ Except for centrally authorised product(s)

⁵⁷ 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

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

PRAC Rapporteur: Mari Thorn

Scope: Substantial amendment to a protocol for an evaluation of the long-term effects of evinacumab treatment in patients with homozygous familial hypercholesterolemia (HoFH): safety outcomes in patients with HoFH who are ≥ 12 years old; frequency and outcomes of pregnancy in female patients with HoFH; atherosclerosis process over time in patients with HoFH who undergo cardiovascular imaging (as data allow); frequency of cardiovascular imaging of patients with HoFH

17.1.2. Valproate⁵⁹ (NAP) - EMEA/H/N/PSP/J/0074.6

Applicant: Sanofi-Aventis Recherche & Développement

PRAC Rapporteur: Jean-Michel Dogné

Scope: Second interim report: Observational study to evaluate and identify the best practices for switching of valproate in clinical practice

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁰

17.2.1. Avacopan - TAVNEOS (CAP) - EMEA/H/C/005523/MEA 002.2

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002.1 [protocol and feasibility report for study CS-AVA-2022-0016 (listed as category 3 study in the RMP): avacopan real world evidence in anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis - characterisation of the safety concerns of avacopan (i.e. liver injury, serious infections, malignancies and cardiovascular events) beyond the known safety profile based on clinical trial data limited to 52 weeks of exposure] as per request for supplementary information (RSI) adopted in December 2022

17.2.2. Ciltacabtagene autoleucl - CARVYKTI (CAP) - EMEA/H/C/005095/MEA 007.1

Applicant: Janssen-Cilag International NV, ATMP⁶¹

PRAC Rapporteur: Jo Robays

Scope: 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

17.2.3. Elasmoran - SPIKEVAX (CAP) - EMEA/H/C/005791/MEA 065.2

Applicant: Moderna Biotech Spain, S.L.

PRAC Rapporteur: Marie Louise Schougaard Christiansen

⁵⁹ Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpriomide, valproate bismuth, calcium valproate, valproate magnesium

⁶⁰ 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

⁶¹ Advanced therapy medicinal product

Scope: Submission of a revised protocol for study mRNA-1273-P910: clinical course, outcomes and risk factors of myocarditis following administration of mRNA-1273 alongside with the second interim report of the study

17.2.4. Pitolisant - OZAWADE (CAP) - EMEA/H/C/005117/MEA 003

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Submission of a protocol for study P21-02: A multi-center, observational prospective PASS to compare the cardiovascular risks and long-term safety of OZAWADE in patients with obstructive sleep apnoea treated or not by primary therapy and exposed or not to OZAWADE when used in routine medical practice

17.2.5. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 002

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a protocol for study I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study to evaluate the incidence of pancreatic malignancy among patients with type 2 diabetes mellitus (T2DM) treated with tirzepatide and to compare the incidence of pancreatic malignancy among patients treated with tirzepatide to patients treated with alternative treatments for clinical indications approved for GLP-1 Ras in Europe

17.2.6. Tirzepatide - MOUNJARO (CAP) - EMEA/H/C/005620/MEA 005

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of a protocol for study I8F-MC-B013: A database linkage study to evaluate the important potential risk of medullary thyroid cancer

17.2.7. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 062

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

17.3. Results of PASS imposed in the marketing authorisation(s)⁶²

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁶³

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

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

17.5.1. Coronavirus (COVID-19) vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (CAP) - EMEA/H/C/005675/MEA 006.8

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Semi-annual report for study D8110C00003 (C-VIPER): COVID-19 Vaccines International Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy (Period covered 01/06/2022-30/11/2022)

17.5.2. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.4

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: 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

17.5.3. Hydroxycarbamide - SIKLOS (CAP) - EMEA/H/C/000689/MEA 035

Applicant: Addmedica

⁶² In accordance with Article 107p-q of Directive 2001/83/EC

⁶³ 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

PRAC Rapporteur: Jo Robays

Scope: Submission of an interim report for study ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea (#2 _V1.0)

17.5.4. Ketoconazole - KETOCONAZOLE HRA (CAP) - EMEA/H/C/003906/ANX 002.10

Applicant: HRA Pharma Rare Diseases

PRAC Rapporteur: Željana Margan Koletić

Scope: MAH's response to ANX 002.9 [Fifth interim annual report for a prospective, multi-country, observational registry study to collect clinical information on patients with endogenous Cushing's syndrome exposed to ketoconazole using the existing European registry on Cushing's syndrome (ERCUSYN) to assess drug utilisation pattern and to document the safety (e.g. hepatotoxicity, QT prolongation) and effectiveness of ketoconazole] as per the request for supplementary information (RSI) adopted in January 2023

17.5.5. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.5

Applicant: Bayer AG

PRAC Rapporteur: Gabriele Maurer

Scope: 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 [final clinical study report (CSR) expected in December 2021]

17.5.6. Ruriocog alfa pegol - ADYNOVI (CAP) - EMEA/H/C/004195/ANX 002.2

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study SHP660-403: a PASS to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs

17.5.7. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 010.6

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Fourth interim report for study C4591012: clinical study to assess the occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine

17.6. Others

17.6.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.5

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Follow-up from ANX 010.4: The provision of answers to questions about the feasibility report of the non-interventional PASS to investigate drug utilization and safety monitoring patterns for LEMTRADA (Alemtuzumab)

17.6.2. Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 028.4

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 028.3 [MAH's request for cancelling the study PGL18-001: a retrospective drug utilisation study (DUS) through a chart review across four major EU countries [final study report expected by Q2 2020], as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in May 2018 (EMA/H/A-20/1460)] as per the request for supplementary information (RSI) adopted in November 2022

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. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/S/0045 (without RMP)

Applicant: Laboratoires Delbert

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual reassessment of the marketing authorisation

18.1.2. Tagraxofusp - ELZONRIS (CAP) - EMEA/H/C/005031/S/0020 (without RMP)

Applicant: Stemline Therapeutics B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Belantamab mafodotin - BLENREP (CAP) - EMEA/H/C/004935/R/0017 (with RMP)

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.2. Bulevirtide - HEPCLUDEX (CAP) - EMEA/H/C/004854/R/0024 (without RMP)

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Conditional renewal of the marketing authorisation

18.2.3. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0015 (without RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.2.4. Idecabtagene vicleucel - ABECMA (CAP) - EMEA/H/C/004662/R/0029 (without RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG, ATMP⁶⁴

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.5. Imlifidase - IDEFIRIX (CAP) - EMEA/H/C/004849/R/0014 (without RMP)

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

⁶⁴ Advanced therapy medicinal product

18.2.6. Pretomanid - DOVPRELA (CAP) - EMEA/H/C/005167/R/0015 (without RMP)

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.7. Valoctocogene roxaparvovec - ROCTAVIAN (CAP) - EMEA/H/C/005830/R/0003 (without RMP)

Applicant: BioMarin International Limited, ATMP⁶⁵

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Abemaciclib - VERZENIOS (CAP) - EMEA/H/C/004302/R/0025 (without RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.2. Binimetinib - MEKTOVI (CAP) - EMEA/H/C/004579/R/0024 (without RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Inês Ribeiro-Vaz

Scope: 5-year renewal of the marketing authorisation

18.3.3. Buprenorphine - BUVIDAL (CAP) - EMEA/H/C/004651/R/0021 (with RMP)

Applicant: Camurus AB

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/R/0027 (without RMP)

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.5. Deferiprone - DEFERIPRONE LIPOMED (CAP) - EMEA/H/C/004710/R/0011 (with RMP)

Applicant: Lipomed GmbH

⁶⁵ Advanced therapy medicinal product

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.6. Doravirine - PIFELTRO (CAP) - EMEA/H/C/004747/R/0027 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.7. Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - EMEA/H/C/004746/R/0034 (without RMP)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.8. Encorafenib - BRAFTOVI (CAP) - EMEA/H/C/004580/R/0029 (without RMP)

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Rugile Pilviniene

Scope: 5-year renewal of the marketing authorisation

18.3.9. Gefitinib - GEFITINIB MYLAN (CAP) - EMEA/H/C/004826/R/0008 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

18.3.10. Lenalidomide - LENALIDOMIDE ACCORD (CAP) - EMEA/H/C/004857/R/0021 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Tiphaine Vaillant

Scope: 5-year renewal of the marketing authorisation

18.3.11. Pegfilgrastim - PELGRAZ (CAP) - EMEA/H/C/003961/R/0040 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pegfilgrastim - ZIEXTENZO (CAP) - EMEA/H/C/004802/R/0025 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.13. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0046 (without RMP)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: 5-year renewal of the marketing authorisation

18.3.14. Vigabatrin - KIGABEQ (CAP) - EMEA/H/C/004534/R/0012 (with RMP)

Applicant: ORPHELIA Pharma SAS

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.15. Vonicog alfa - VEYVONDI (CAP) - EMEA/H/C/004454/R/0027 (with RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Mari Thorn

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 11-14 April 2023 meeting. Participants marked with "a" attended the plenary session while those marked with "b" attended the ORGAM

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus ^a	Chair	The Netherlands	No interests declared	
Jan Neuhauser ^a	Member	Austria	No interests declared	
Sonja Hrabcik ^a	Alternate	Austria	No interests declared	
Jean-Michel Dogné ^{a, b}	Member	Belgium	No interests declared	
Jo Robays ^a	Alternate	Belgium	No interests declared	
Maria Popova-Kiradjieva ^{a, b}	Member	Bulgaria	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Nikica Mirošević Skvrce ^a	Member	Croatia	No interests declared	
Zeljana Margan Koletić ^a	Alternate	Croatia	No interests declared	
Elena Kaisis ^{a, b}	Member	Cyprus	No interests declared	
Panagiotis Psaras ^{a, b}	Alternate	Cyprus	No interests declared	
Eva Jirsová ^{a, b}	Member	Czechia	No interests declared	
Jana Lukacisinova ^{a, b}	Alternate	Czechia	No interests declared	
Anette Kristine Stark ^{a, b}	Member	Denmark	No interests declared	
Marie Louise Schougaard Christiansen ^{a, b}	Alternate	Denmark	No interests declared	
Kroot Aab ^a	Alternate	Estonia	No interests declared	
Kirsti Villikka ^a	Member	Finland	No interests declared	
Kimmo Jaakkola ^{a, b}	Alternate	Finland	No interests declared	
Tiphaine Vaillant ^{a, b}	Member	France	No interests declared	
Nathalie Gault ^a	Alternate	France	No interests declared	
Martin Huber ^{a, b}	Member (Vice-Chair)	Germany	No interests declared	
Gabriele Maurer ^{a, b}	Alternate	Germany	No participation in final deliberations and voting on:	15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003 985/II/0125/G
Sofia Trantza ^{a, b}	Member	Greece	No interests declared	
Georgia Gkegka ^{a, b}	Alternate	Greece	No interests declared	
Julia Pallos ^a	Member	Hungary	No participation in final	6.1.7. Idecabtagene vicleucel - ABECMA (CAP) -

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	<p>PSUSA/00010954/202209</p> <p>15.3.15. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/II/0100</p> <p>15.3.18. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/II/0123</p> <p>15.3.22. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0125/G</p> <p>15.3.23. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0047, Orphan</p> <p>15.3.29. Thalidomide - THALIDOMIDE BMS (CAP) - EMEA/H/C/000823/II/0076</p> <p>18.2.4. Idecabtagene vicleucef - ABECMA (CAP) - EMEA/H/C/004662/R/0029 (without RMP)</p>
Melinda Palfi ^b	Alternate	Hungary	No interests declared	
Guðrún Stefánsdóttir ^b	Member	Iceland	No participation in final deliberations and voting on:	<p>4.3.3. Evolocumab – REPATHA (CAP) - EMEA/H/C/003766/SDA/017</p> <p>15.2.6.</p>

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/II/0059 16.1.26. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/202209 "
Gudrun Thengilsdottir ^a	Alternate	Iceland	No restrictions applicable to this meeting	
Eamon O Murchu ^{a, b}	Alternate	Ireland	No interests declared	
Amelia Cupelli ^{a, b}	Member	Italy	No interests declared	
Valentina Di Giovanni ^{a, b}	Alternate	Italy	No interests declared	
Zane Neikena ^{a, b}	Member	Latvia	No interests declared	
Rugile Pilviniene ^a	Member	Lithuania	No interests declared	
Lina Seibokiene ^a	Alternate	Lithuania	No restrictions applicable to this meeting	
Nadine Petitpain ^b	Member	Luxembourg	No restrictions applicable to this meeting	
Anne-Cécile Vuillemin ^a	Alternate	Luxembourg	No interests declared	
Benjamin Micallef ^a	Alternate	Malta	No interests declared	
Menno van der Elst ^a	Member	Netherlands	No interests declared	
Liana Gross-Martirosyan ^{a, b}	Alternate	Netherlands	No interests declared	
David Olsen ^{a, b}	Member	Norway	No participation	15.3.25. Riociguat - ADEMPAS

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			in final deliberations and voting on:	(CAP) - EMEA/H/C/002 737/II/0037 16.2.3. Octocog alfa - ADVATE (CAP); KOGENATE BAYER (CAP); KOVALTRY (CAP); NAP - PSUSA/000022 00/202208 16.3.6. Drospirenone, ethinylestradiol (NAP) - PSUSA/000102 17/202209 17.5.2. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004 054/MEA 003.4 17.5.5. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003 825/MEA 004.5 18.3.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004 054/R/0027 (without RMP)
Karen Pernille Harg ^{a, b}	Alternate	Norway	No interests declared	
Adam Przybylkowski ^a	Member	Poland	No interests declared	
Ana Sofia Diniz Martins ^a	Member	Portugal	No interests declared	
Ines Ribeiro-Vaz ^a	Alternate	Portugal	No interests declared	
Roxana Dondera ^{a, b}	Member	Romania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Irina Sandu ^a	Alternate	Romania	No interests declared	
Anna Mareková ^{a, b}	Member	Slovakia	No interests declared	
Miroslava Gocova ^{a, b}	Alternate	Slovakia	No interests declared	
Polona Golmajer ^{a, b}	Member	Slovenia	No interests declared	
Milena Radoha-Bergoc ^b	Alternate	Slovenia	No participation in final deliberations and voting on:	14.1.4. Pramipexole – MIRAPEXIN (CAP); OPRYMEA (CAP); PRAMIPEXOLE TEVA (CAP); SIFROL (CAP); (NAP)
Maria del Pilar Rayon ^{a, b}	Member	Spain	No interests declared	
Monica Martinez Redondo ^{a, b}	Alternate	Spain	No interests declared	
Ulla Wändel Liminga ^{a, b}	Member	Sweden	No interests declared	
Mari Thorn ^{a, b}	Alternate	Sweden	No restrictions applicable to this meeting	
Annalisa Capuano ^a	Member	Independent scientific expert	No interests declared	
Milou Daniel Drici ^b	Member	Independent scientific expert	No interests declared	
Maria Teresa Herdeiro ^a	Member	Independent scientific expert	No interests declared	
Tania Schink ^a	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.4. Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide – TRULICITY (CAP); exenatide – BYDUREON (CAP), BYETTA (CAP); insulin degludec, liraglutide –

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				XULTOPHY (CAP); liraglutide – SAXENDA (CAP), VICTOZA (CAP); lixisenatide - LYXUMIA (CAP); semaglutide – OZEMPIC (CAP), RYBELSUS (CAP), WEGOVY (CAP) 7.2.2. Solriamfetol - SUNOSI (CAP) - EMEA/H/C/004 893/MEA 002.2)
Hedvig Nordeng ^a	Member	Independent scientific expert	No interests declared	
Roberto Frontini ^{a, b}	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	
Salvatore Messina ^a	Alternate	Healthcare Professionals' Representative	No interests declared	
Marko Korenjak ^a	Alternate	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	15.2.4. Somatropin - NUTROPINAQ (CAP) - EMEA/H/C/000 315/II/0077
Els Beghein ^a	Expert	Belgium	No interests declared	
Christelle Bizimungu ^a	Expert	Belgium	No interests declared	
Ingrid Bourges ^a	Expert	Belgium	No interests declared	
Laurence de Fays ^a	Expert	Belgium	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Jamila Hamdani ^a	Expert	Belgium	No interests declared	
Barbara Kovacic ^a	Expert	Croatia	No interests declared	
Petar Mas ^b	Expert	Croatia	No interests declared	
Anna Kroupova ^a	Expert	Czechia	No interests declared	
Petra Vackova ^a	Expert	Czechia	No interests declared	
Hanna Belcik Christensen ^a	Expert	Denmark	No interests declared	
Marianne Hald Clemmensen ^a	Expert	Denmark	No restrictions applicable to this meeting	
Karin Erneholm ^a	Expert	Denmark	No restrictions applicable to this meeting	
Kirsten Egebjerg Juul ^a	Expert	Denmark	No interests declared	
Moritz Sander ^a	Expert	Denmark	No interests declared	
Ane Blicher Schelde ^a	Expert	Denmark	No interests declared	
Barbara Blicher Thomsen ^a	Expert	Denmark	No interests declared	
Chau Minh Tran ^a	Expert	Denmark	No interests declared	
Caroline Marie Voss ^a	Expert	Denmark	No interests declared	
Julia Maslovskaja ^a	Expert	Estonia	No interests declared	
Katia Chemala ^a	Expert	France	No interests declared	
Samuel Crommelynck ^a	Expert	France	No interests declared	
Vincent Gazin ^a	Expert	France	No interests declared	
Nathalie Morgensztejn ^a	Expert	France	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marie-Caroline Pesquidous ^a	Expert	France	No restrictions applicable to this meeting	
Nicole Bick ^a	Expert	Germany	No interests declared	
Jelena Katic ^a	Expert	Germany	No interests declared	
Dennis Lex ^a	Expert	Germany	No interests declared	
Anne-Charlotte Lübow ^a	Expert	Germany	No interests declared	
Dario Ortiz ^a	Expert	Germany	No interests declared	
Wiebke Seemann-Roch ^a	Expert	Germany	No interests declared	
Ronan Grimes ^a	Expert	Ireland	No interests declared	
Paul ten Berg ^a	Expert	Netherlands	No interests declared	
Marcel Kwa ^a	Expert	Netherlands	No interests declared	
Maria Vanenburg ^a	Expert	Netherlands	No interests declared	
María Martínez ^a	Expert	Spain	No interests declared	
Charlotte Backman ^{a,b}	Expert	Sweden	No interests declared	
Karin Hellgren ^a	Expert	Sweden	No interests declared	
Kristina Magnusson Lundqvist ^a	Expert	Sweden	No interests declared	
Jessica Mwinyi ^a	Expert	Sweden	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations, see:

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>