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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 07-10 March 2022

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

Note on access to documents

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Table of contents

1. Introduction 13

1.1. Welcome and declarations of interest of members, alternates and experts 13

1.2. Agenda of the meeting on 07-10 March 2022 13

1.3. Minutes of the previous meeting on 07-10 February 2022 13

2. EU referral procedures for safety reasons: urgent EU procedures 13

2.1. Newly triggered procedures 13

2.2. Ongoing procedures 13

2.3. Procedures for finalisation 14

3. EU referral procedures for safety reasons: other EU referral procedures 14

3.1. Newly triggered procedures 14

3.2. Ongoing procedures 14

3.3. Procedures for finalisation 14

3.4. Re-examination procedures 14

3.5. Others 14

4. Signals assessment and prioritisation 14

4.1. New signals detected from EU spontaneous reporting systems 14

4.1.1. Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP) serotonin-norepinephrine reuptake inhibitor (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP) mirtazapine (NAP); vortioxetine - BRINTELLIX (CAP) 14

4.2. New signals detected from other sources 15

4.3. Signals follow-up and prioritisation 15

4.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/SDA/012 15

4.3.2. Cannabidiol – EPIDYOLEX (CAP); calcineurin inhibitors: ciclosporin (NAP); tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/SDA/031, ENVARSUS (CAP) - EMEA/H/C/002655/SDA/003, MODIGRAF (CAP) - EMEA/H/C/000954/SDA/023, TACFORIUS (CAP) - EMEA/H/C/004435/SDA/004, NAP mammalian target of rapamycin (mTOR) inhibitors: everolimus – AFINITOR (CAP) - EMEA/H/C/001038/SDA/033, VOTUBIA (CAP) - EMEA/H/C/002311/SDA/033, NAP; sirolimus – RAPAMUNE (CAP) - EMEA/H/C/002311/SDA/055; temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/SDA/038, NAP 16

4.3.3. Elasomeran (previously coronavirus (COVID-19) mRNA vaccine (nucleoside-modified))- SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/052.1; tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/051 17

4.3.4. Sacubitril, valsartan – ENTRESTO (CAP) - EMEA/H/C/004062/SDA/010, NEPARVIS (CAP) - EMEA/H/C/004343/SDA/008 18

4.4. Variation procedure(s) resulting from signal evaluation 18

5. Risk management plans (RMPs) 18

5.1. Medicines in the pre-authorisation phase 18

5.1.1. Eptacog beta (activated) - - EMEA/H/C/005655 19

5.1.2. Melphalan flufenamide - EMEA/H/C/005681, Orphan 19

5.1.3. Mitapivat - - EMEA/H/C/005540, Orphan 19

5.1.4. Tabelecleucel - - EMEA/H/C/004577, PRIME, Orphan 19

5.1.5. Tezepelumab - - EMEA/H/C/005588 19

5.1.6. Tixagevimab, cilgavimab - - EMEA/H/C/005788 19

5.2. Medicines in the post-authorisation phase – PRAC-led procedures 19

5.3. Medicines in the post-authorisation phase – CHMP-led procedures 19

5.3.1. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/II/0035 19

5.3.2. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0070 20

5.3.3. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0056 21

5.3.4. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0061, Orphan 22

5.4. Medicines in the post-authorisation phase – CHMP-led procedures 22

6. Periodic safety update reports (PSURs) 23

6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only 23

6.1.1. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202108 23

6.1.2. Desloratadine, pseudoephedrine - AERINAZE (CAP) - PSUSA/00000963/202107 23

6.1.3. Efavirenz, emtricitabine, tenofovir – ATRIPLA - PSUSA/00001201/202107 24

6.1.4. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/202108 25

6.1.5. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202108 25

6.1.6. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202108 26

6.2. (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) 27

6.2.1. Desloratadine - AERIUS (CAP); AZOMYR (CAP); DASSELTA (CAP); DESLORATADINE ACTAVIS (CAP); DESLORATADINE RATIOPHARM (CAP); DESLORATADINE TEVA (CAP); NEOCLARITYN (CAP); NAP - PSUSA/00000962/202107 27

6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only 28

6.3.1. Amlodipine, rosuvastatin (NAP); amlodipine, perindopril, rosuvastatin (NAP) - PSUSA/00010434/202107 28

6.3.2. Leuprorelin (NAP) - PSUSA/00010877/202107 29

6.3.3. Magnesium sulfate, sodium sulfate, potassium sulfate (NAP) - PSUSA/00010239/202108 . 30

6.3.4. Montelukast (NAP) - PSUSA/00002087/202107 30

6.4. Follow-up to PSUR/PSUSA procedures 31

6.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/LEG 057 31

6.4.2. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 009 32

6.5. Variation procedure(s) resulting from PSUSA evaluation 32
6.6. Expedited summary safety reviews 32
6.6.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.8 32
7. Post-authorisation safety studies (PASS) 33
7.1. Protocols of PASS imposed in the marketing authorisation(s) 33
7.2. Protocols of PASS non-imposed in the marketing authorisation(s) 33
7.3. Results of PASS imposed in the marketing authorisation(s) 33
7.3.1. Direct acting antivirals (DAAV): Dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir - ZEPATIER (CAP); glecaprevir, pibrentasvir - MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir, peritepreviir, ritonavir - VIEKIRAX (CAP); sofosbuvir - SOVALDI (CAP); sofosbuvir, velpatasvir - EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/PSR/J/0038 33
7.4. Results of PASS non-imposed in the marketing authorisation(s) 35
7.4.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0031, Orphan 35
7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation 35
7.5.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.13 36
7.6. Others 36
7.7. New Scientific Advice 36
7.8. Ongoing Scientific Advice 36
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. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0029 (with RMP) 37
8.2. Conditional renewals of the marketing authorisation 37
8.3. Renewals of the marketing authorisation 37
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 38
10.4. Scientific Advice 38

11. Other safety issues for discussion requested by the Member States 38

11.1. Safety related variations of the marketing authorisation 38

11.2. Other requests 38

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

12.3.1. EMA Emergency task force (ETF) - PRAC nominations 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 39

12.5.1. International Conference on Harmonisation (ICH) E2D(R1) - Post-approval safety data management: definitions and standards for expedited reporting 39

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

12.9. 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) 40

12.10.3. PSURs repository 40

12.10.4. Union reference date list – consultation on the draft list 40

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 41

12.13.1. Activities related to the confirmation of full functionality 41

12.13.2. EudraVigilance – annual report 2021 41

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
12.15. 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
12.17. Renewals, conditional renewals, annual reassessments 42
12.18. Risk communication and transparency 42
12.18.1. Public participation in pharmacovigilance 42
12.18.2. Safety communication 42
12.19. Continuous pharmacovigilance 42
12.19.1. Incident management 42
12.20. Impact of pharmacovigilance activities 42
12.21. Others 43
12.21.1. Data analysis and real-world interrogation network (DARWIN EU) – introduction of the coordination centre and next steps for real-world evidence (RWE) 43
12.21.2. Data protection notice – processing of scientific Committees (CxMP) members/alternates' contact details 43
12.21.3. Pharmacovigilance business team - activities and work plan 43
13. Any other business 43
14. Annex I – Signals assessment and prioritisation 43
14.1. New signals detected from EU spontaneous reporting systems 43
14.2. New signals detected from other sources 44
14.2.1. Pneumococcal polysaccharide vaccine (23 serotypes) (NAP) 44
14.2.2. Tocilizumab - ROACTEMRA (CAP) 44
15. Annex I – Risk management plans 44
15.1. Medicines in the pre-authorisation phase 44
15.1.1. Doxorubicin hydrochloride - - EMEA/H/C/005330 44
15.1.2. Ertapenem - - EMEA/H/C/005815 44
15.1.3. Ganirelix - - EMEA/H/C/005641 44
15.1.4. Sitagliptin, metformin hydrochloride - - EMEA/H/C/005850 44
15.1.5. Sugammadex - - EMEA/H/C/005760 45
15.2. Medicines in the post-authorisation phase – PRAC-led procedures 45
15.2.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2210/0076; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2210/0100; dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2210/0028; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2210/0041 45

15.2.2. Duloxetine - DULOXETINE MYLAN (CAP), NAP - EMEA/H/C/003981/WS2214/0029 45
15.2.3. Fentanyl - EFFENTORA (CAP), NAP - EMEA/H/C/000833/WS2212/0060 45
15.2.4. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/II/0054 46
15.2.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0026, Orphan 46
15.2.6. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0037 46
15.2.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0038 46
15.2.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0087 47
15.3. Medicines in the post-authorisation phase – CHMP-led procedures 47
15.3.1. Agalsidase alfa - REPLAGAL (CAP) - EMEA/H/C/000369/II/0117 47
15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0064 47
15.3.3. Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/II/0008/G, Orphan 48
15.3.4. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - EMEA/H/C/004449/X/0040/G 48
15.3.5. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0099, Orphan 48
15.3.6. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS2150/0146; PLAVIX (CAP) - EMEA/H/C/000174/WS2150/0145; clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP) - EMEA/H/C/001143/WS2150/0060 49
15.3.7. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/II/0018/G, Orphan 49
15.3.8. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0056, Orphan 49
15.3.9. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/X/0079/G 49
15.3.10. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0057 50
15.3.11. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0010/G, Orphan 50
15.3.12. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0011/G, Orphan 50
15.3.13. Gemtuzumab ozogamicin - MYLOTARG (CAP) - EMEA/H/C/004204/II/0024, Orphan 51
15.3.14. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0006, Orphan 51
15.3.15. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/II/0042 51
15.3.16. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/II/0025, Orphan 51
15.3.17. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0024, Orphan 52
15.3.18. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/II/0030, Orphan 52
15.3.19. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0002, Orphan 52
15.3.20. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0005, Orphan 52
15.3.21. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0002/G 53
15.3.22. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0026 53
15.3.23. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - EMEA/H/C/005267/II/0006 . 53
15.3.24. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0188 53
15.3.25. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0053 54
15.3.26. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0044, Orphan 54

15.3.27. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0014 54
15.3.28. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/II/0010, Orphan 54
15.3.29. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0015/G 55
15.3.30. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/II/0017/G, Orphan 55
16. Annex I - Periodic safety update reports (PSURs) 55
16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only 56
16.1.1. Aflibercept - ZALTRAP (CAP) - PSUSA/00010019/202108 56
16.1.2. Agalsidase alfa - REPLAGAL (CAP) - PSUSA/00000069/202108 56
16.1.3. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202108 56
16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202107 56
16.1.5. Baloxavir marboxil - XOFLUZA (CAP) - PSUSA/00010895/202108 56
16.1.6. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202108 57
16.1.7. Bempedoic acid- NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202108 57
16.1.8. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202108 57
16.1.9. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202107 57
16.1.10. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202107 57
16.1.11. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/202108 57
16.1.12. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - PSUSA/00010916/202108 57
16.1.13. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202107 58
16.1.14. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - PSUSA/00010701/202108 58
16.1.15. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202107 58
16.1.16. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202108 58
16.1.17. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202108 58
16.1.18. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202108 58
16.1.19. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202108 58
16.1.20. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202108 59
16.1.21. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202108 59
16.1.22. Hydrocortisone - ALKINDI (CAP) - PSUSA/00010674/202108 59
16.1.23. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/202107 59
16.1.24. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/202107 59
16.1.25. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202108 59
16.1.26. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/00001759/202107 59
16.1.27. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202108 60
16.1.28. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202108 60

16.1.29. Lipegfilgrastim - LONQUEX (CAP) - PSUSA/00010111/202107 60
16.1.30. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202107 60
16.1.31. Maraviroc - CELSENTRI (CAP) - PSUSA/00001934/202108 60
16.1.32. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202108 60
16.1.33. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202108 60
16.1.34. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202108 61
16.1.35. Pioglitazone - ACTOS (CAP), GLUSTIN; pioglitazone, glimepiride – TANDEMACT (CAP); pioglitazone, metformin - COMPETACT (CAP); GLUBRAVA (CAP) - PSUSA/00002417/202107 61
16.1.36. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202108 61
16.1.37. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202108 61
16.1.38. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/202107 61
16.1.39. Smallpox vaccine (live, modified vaccinia Ankara virus) - IMVANEX (CAP) - PSUSA/00010119/202107 61
16.1.40. Tisagenlecleucel - KYMRIAH (CAP) - PSUSA/00010702/202108 62
16.1.41. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202107 62
16.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) 62
16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only 62
16.3.1. Alprostadil (NAP) - PSUSA/00010021/202107 62
16.3.2. Budesonide, salmeterol (NAP) - PSUSA/00010511/202107 62
16.3.3. Cefuroxime sodium (NAP) - PSUSA/00010206/202105 62
16.3.4. Everolimus (NAP) - PSUSA/00010269/202107 62
16.3.5. Fluocinolone acetonide (NAP) - PSUSA/00010224/202108 63
16.3.6. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/202107 63
16.3.7. Human plasma protease C1 inhibitor (NAP) - PSUSA/00010163/202108 63
16.3.8. Indium (^{111}In) chloride (NAP); indium (^{111}In) oxine (NAP) - PSUSA/00001734/202107 63
16.3.9. Lovastatin (NAP) - PSUSA/00010051/202107 63
16.3.10. Pilocarpine, timolol (NAP) - PSUSA/00002408/202107 63
16.3.11. Tiapride (NAP) - PSUSA/00002944/202107 64
16.3.12. Timolol (NAP) - PSUSA/00010439/202107 64
16.4. Follow-up to PSUR/PSUSA procedures 64
16.5. Variation procedure(s) resulting from PSUSA evaluation 64
16.5.1. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0025 64
17. Annex I – Post-authorisation safety studies (PASS) 64
17.1. Protocols of PASS imposed in the marketing authorisation(s) 64
17.1.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/PSA/S/0083 64
17.1.2. Valproate (NAP) - EMEA/H/N/PSP/J/0072.6 65
17.1.3. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSA/S/0081.1 65

17.2. Protocols of PASS non-imposed in the marketing authorisation(s) 65
17.2.1. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 002 65
17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 003 65
17.2.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004 66
17.2.4. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/MEA 051.1 66
17.2.5. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 011.1 66
17.2.6. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001.1 66
17.2.7. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001.1 67
17.2.8. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.7 67
17.2.9. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 003.2 67
17.2.10. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/MEA 004 67
17.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005 68
17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017.1 68
17.2.13. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.2 68
17.2.14. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.1 68
17.2.15. Tralokinumab - ADTRALZA (CAP) - EMEA/H/C/005255/MEA 001 69
17.2.16. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 014 69
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. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0068 69
17.4.2. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0033, Orphan 69
17.4.3. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0075 70
17.4.4. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS2216/0052; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/WS2216/0049; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS2216/0064 70
17.4.5. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0033 70
17.4.6. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0028 70
17.4.7. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0105 70
17.4.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0111 71
17.4.9. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0047 71
17.4.10. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0073 71
17.4.11. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS2222/0077; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS2222/0104; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS2222/0064; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS2222/0054 71
17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation 71
17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.2 71

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.16 72
17.5.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.16 72
17.5.4. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.3 72
17.5.5. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.13 72
17.5.6. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/MEA 002.5 73
17.5.7. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.1 73
17.5.8. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.3 73
17.5.9. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.3 73
17.5.10. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.3 73
17.5.11. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.8 74
17.5.12. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.10 74
17.5.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.14 74
17.5.14. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007.2 74
17.5.15. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.3 74
17.5.16. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.9 75
17.5.17. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.12 75
17.5.18. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.13 75
17.5.19. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059.2 75
17.5.20. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.3 75
17.5.21. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.2 76
17.5.22. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/MEA 003.6 76
17.5.23. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.4 76
17.5.24. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.4 76
17.6. Others 77
17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.3 77
17.6.2. Darvadstrocel - ALOFISEL (CAP) - EMEA/H/C/004258/MEA 007 77
17.6.3. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.4 77
17.6.4. Human C1-esterase inhibitor - CINRYZE (CAP) - EMEA/H/C/001207/MEA 021 77
17.6.5. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.1 77
17.6.6. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.1 78
17.6.7. Tralokinumab - ADTRALZA (CAP) - EMEA/H/C/005255/MEA 002 78
17.7. New Scientific Advice 78
17.8. Ongoing Scientific Advice 78
17.9. Final Scientific Advice (Reports and Scientific Advice letters) 78
18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments 78
18.1. Annual reassessments of the marketing authorisation 79

18.1.1. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0042 (without RMP) 79
18.1.2. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0076 (without RMP) 79
18.2. Conditional renewals of the marketing authorisation 79
18.2.1. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0029 (without RMP) 79
18.2.2. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0007 (with RMP) 79
18.2.3. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/R/0021 (without RMP) 79
18.2.4. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/R/0031 (without RMP) 79
18.2.5. Selinexor - NEXPOVIO (CAP) - EMEA/H/C/005127/R/0005 (without RMP) 80
18.3. Renewals of the marketing authorisation 80
18.3.1. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/R/0040 (without RMP) 80
18.3.2. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL MYLAN (CAP) - EMEA/H/C/004240/R/0019 (without RMP) 80
18.3.3. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004250/R/0025 (without RMP) 80
18.3.4. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/R/0032 (without RMP) 80
18.3.5. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/R/0023 (without RMP) 80
18.3.6. Tivozanib - FOTIVDA (CAP) - EMEA/H/C/004131/R/0021 (without RMP) 81
19. Annex II – List of participants 81
20. Annex III - List of acronyms and abbreviations 87
21. Explanatory notes 87

1. Introduction

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

The Chairperson opened the meeting by welcoming all participants. Due to the coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda topics. Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional competing interests were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. 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 07-10 March 2022

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 07-10 February 2022

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

Post-meeting note: the PRAC minutes of the meeting held 07-10 February 2022 were published on the EMA website on 07 November 2022.

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

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 procedures[1]

None

3.5. Others

None

4. Signals assessment and prioritisation[2]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP)
serotonin-norepinephrine reuptake inhibitor (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP)
mirtazapine (NAP); vortioxetine - BRINTELLIX (CAP)

Applicant(s): Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Yentreve), H. Lundbeck A/S (Brintellix), Mylan Pharmaceuticals Limited (Duloxetine Mylan), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of pulmonary hypertension

EPITT 19772 – New signal

[1] Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC
[2] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Lead Member State(s): BE, ES, FR, LT, NL, SE

Background

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are selective serotonin reuptake transporter inhibitors (SSRI). Desvenlafaxine, duloxetine, milnacipran and venlafaxine are serotonin-norepinephrine reuptake inhibitor (SNRIs). Mirtazapine and vortioxetine are (atypical) antidepressants. They are indicated, amongst other indications, in major depressive disorders, anxiety disorders, obsessive compulsive disorder, post-traumatic stress disorder (PTSD) and premenstrual dysphoric disorder.

During routine signal detection activities, a signal of pulmonary hypertension was identified by Germany, based on 93 cases retrieved from EudraVigilance following sertraline or other SSRI use. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the literature and the plausible biological mechanism between pulmonary hypertension (PH) and SSRIs, SNRIs, mirtazapine and vortioxetine, PRAC agreed that further review is warranted, including a systematic review of the literature, available mechanistic data as well as further evaluation of case reports.

PRAC appointed Liana Gross-Martirosyan as Rapporteur for the signal.

Summary of recommendation(s)

- The brand-leader MAHs for citalopram-, desvenlafaxine-, duloxetine-, escitalopram-, fluoxetine-, fluvoxamine-, milnacipran-, mirtazapine-, paroxetine-, sertraline-, venlafaxine- and vortioxetine-containing products should submit to EMA, within 60 days, a cumulative review of cases of new onset PH or worsening of PH. The MAHs should provide available non-clinical data of relevance for assessing a potential risk for PH, including mechanistic data, and discuss their relevance for humans.
- EMA/PRAC will retrieve and review available published clinical and epidemiological studies and other relevant publications with focus on new onset PH, worsening of PH and mechanistic studies.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2. New signals detected from other sources

See Annex I 14.2.

4.3. Signals follow-up and prioritisation

4.3.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/SDA/012

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of vitiligo

EPITT 19737 – Follow-up to November 2021

Background

For background information, see PRAC minutes November 2021[3].

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the responses submitted by the MAH and the Rapporteur's assessment, PRAC considered that a causal relationship between vitiligo and alemtuzumab is at least a reasonable possibility. Therefore, PRAC agreed that vitiligo should be added to the product information as an undesirable effect with a frequency 'uncommon'.

Summary of recommendation(s)

- The MAH for Lemtrada (alemtuzumab) should submit to EMA, within 60 days, a variation to amend[4] the product information.

For the full PRAC recommendation, see EMA/PRAC/139810/2022 published on 04 April 2022 on the EMA website.

4.3.2. Cannabidiol – EPIDYOLEX (CAP); calcineurin inhibitors[5]: ciclosporin (NAP); tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/SDA/031, ENVARSUS (CAP) - EMEA/H/C/002655/SDA/003, MODIGRAF (CAP) - EMEA/H/C/000954/SDA/023, TACFORIUS (CAP) - EMEA/H/C/004435/SDA/004, NAP mammalian target of rapamycin (mTOR) inhibitors[6]: everolimus – AFINITOR (CAP) - EMEA/H/C/001038/SDA/033, VOTUBIA (CAP) - EMEA/H/C/002311/SDA/033, NAP; sirolimus – RAPAMUNE (CAP) - EMEA/H/C/002311/SDA/055; temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/SDA/038, NAP

Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), GW Pharma (International) B.V. (Epidyolex), Novartis Europharm Limited (Afinitor, Votubia), Pfizer Europe MA EEIG (Rapamune, Torisel), Teva B.V. (Tacforius), various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity

EPITT 19614 – Follow-up to June 2021

Background

For background information, see PRAC minutes June 2021.

The MAHs for originator medicinal products containing systemic calcineurin inhibitors (ciclosporin, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus, temsirolimus) respectively replied to the request for information on the signal of

[3] Held 25-28 October 2021
[4] Update of SmPC section 4.8. The package leaflet is to be updated accordingly
[5] For systemic use
[6] For systemic use

drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity and the responses were assessed by the Rapporteur.

Summary of recommendation(s)

Having considered the available evidence from the literature, the responses submitted by the relevant MAHs, a recent drug-drug interaction study between cannabidiol and everolimus together with the Rapporteur's assessment, PRAC agreed there is sufficient evidence to recommend the inclusion of information regarding the risk of interaction with cannabidiol in the product information of calcineurin inhibitor- and mTOR inhibitor-containing products.

Summary of recommendation(s)

- The MAHs of medicinal products for systemic use containing tacrolimus, ciclosporin, everolimus, sirolimus or temsirolimus should submit to EMA or to the National Competent Authorities (NCAs) of the Member States as applicable, within 60 days, a variation to amend[7] the product information.

For the full PRAC recommendation, see EMA/PRAC/139810/2022 published on 04 April 2022 on the EMA website.

4.3.3. Elasomeran (previously coronavirus (COVID-19) mRNA[8] vaccine (nucleoside-modified))- SPIKEVAX (CAP) - EMEA/H/C/005791/SDA/052.1; tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/SDA/051

Applicant(s): BioNTech Manufacturing GmbH (Comirnaty), Moderna Biotech Spain, S.L. (Spikevax)

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Scope: Signal of capillary leak syndrome

EPITT 19743 – Follow-up to January 2022

Background

For background information, see PRAC minutes January 2022.

The MAHs replied to the further request for information on the signal of capillary leak syndrome (CLS) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature, the responses submitted by the MAHs of Comirnaty (tozinameran) and Spikevax (elasomeran) and the Rapporteur's assessment, PRAC agreed to add CLS flare-ups to the product information of Spikevax (elasomeran) as a warning. In addition, PRAC concluded that there is insufficient evidence at this stage to amend the product information of Comirnaty (tozinameran).

Summary of recommendation(s)

- The MAH for Spikevax (elasomeran) should submit to EMA, within 30 days, a variation to amend[9] the product information.

[7] Update of SmPC sections 4.4 and 4.5. The package leaflet is to be updated accordingly
[8] Messenger ribonucleic acid
[9] Update of SmPC section 4.4. The package leaflet is to be updated accordingly

- The MAH for Comirnaty (tozinameran) should continue to monitor cases of CLS as part of routine safety surveillance.

For the full PRAC recommendation, see EMA/PRAC/139810/2022 published on 04 April 2022 on the EMA website.

4.3.4. Sacubitril, valsartan – ENTRESTO (CAP) - EMEA/H/C/004062/SDA/010, NEPARVIS (CAP) - EMEA/H/C/004343/SDA/008

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of vasoplegia syndrome

EPITT 19739 – Follow-up to November 2021

Background

For background information, see PRAC minutes November 2021[10].

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

Discussion

Having considered the available evidence from EudraVigilance, the literature, the review provided by the MAH and the Rapporteur's assessment, PRAC agreed that there is insufficient evidence at present to establish a causal relationship between the development of vasoplegia syndrome and treatment with sacubitril/valsartan.

Summary of recommendation(s)

- The MAH should continue to monitor cases of vasoplegia syndrome as part of routine safety surveillance.

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.

[10] Held 25-28 October 2021

5.1.1. Eptacog beta (activated) - - EMEA/H/C/005655

Scope: Treatment of bleeding episodes and prevention of bleeding in patients undergoing surgery or invasive procedures, in children and adults congenital haemophilia A or B patients

5.1.2. Melphalan flufenamide - EMEA/H/C/005681, Orphan

Applicant: Oncopeptides AB

Scope: Treatment of multiple myeloma

5.1.3. Mitapivat - - EMEA/H/C/005540, Orphan

Applicant: Agios Netherlands B.V.

Scope: Treatment of pyruvate kinase deficiency

5.1.4. Tabelecleucel - - EMEA/H/C/004577, PRIME, Orphan

Applicant: Atara Biotherapeutics Ireland Limited, ATMP[11]

Scope (accelerated assessment): Treatment of Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV$^+$ PTLD)

5.1.5. Tezepelumab - - EMEA/H/C/005588

Scope: Add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma

5.1.6. Tixagevimab, cilgavimab - - EMEA/H/C/005788

Scope: Prophylaxis of coronavirus disease 2019 (COVID-19) in adults 18 years of age and older

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. Dexmedetomidine - DEXDOR (CAP) - EMEA/H/C/002268/II/0035

Applicant: Orion Corporation

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC in order to add a new warning on mortality in intensive care unit patients ≤ 65 years old, based on results from study SPICE III: an open-label, randomized trial on early sedation with dexmedetomidine in ventilated critically ill

[11] Advanced therapy medicinal product

patients and heterogeneity of treatment effect and based on the completion of post-authorisation measure LEG 16.4 finalised in November 2021. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. A proposal for a direct healthcare professional communication (DHPC) and a communication plan is submitted. The RMP (version 9) is updated accordingly

Background

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

CHMP is evaluating a type II variation to update the product information in order to add a new warning on mortality in intensive care unit patients ≤ 65 years old, based on results from study SPICE III, an open-label, randomised trial on early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes July 2021 and PRAC minutes November 2021[12].

Summary of advice

- The RMP for Dexdor (dexmedetomidine) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 9.1 is submitted.
- The MAH should submit to EMA a proposal for additional pharmacovigilance activity/activities to address important potential risk of 'increased mortality in younger intensive care unit (ICU) patients' as an important potential risk within 180 days following finalisation of the current procedure.
- PRAC agreed on the need and on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution.

5.3.2. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0070

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of the existing indication on chronic lymphocytic leukaemia (CLL) to include combination treatment with venetoclax for previously untreated patients based on efficacy and safety data from: 1) study GLOW: a phase 3 trial testing ibrutinib and venetoclax for people with untreated CLL or small lymphocytic lymphoma (SLL); 2) study PCYC-1142-CA (CAPTIVATE): a phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naïve CLL/SLL. The SmPC sections 4.1, 4.2, 4.8 and 18.4 are updated in accordance. The package leaflet and the RMP (version 18.4) are updated accordingly. the MAH also included a justification to support one year-extension of the marketing protection period

Background

[12] Held 25-28 October 2021

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 of the therapeutic indication for Imbruvica, a centrally authorised product containing ibrutinib, to include combination treatment with venetoclax for previously untreated patients for the existing indication on CLL. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Imbruvica (ibrutinib) in the context of the procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 18.4 is submitted and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The MAH should provide a detailed analysis of all available data to better characterise the 'use in patients with severe cardiac disease' classified as missing information in the list of safety concerns.

5.3.3. Naltrexone hydrochloride, bupropion hydrochloride - MYSIMBA (CAP) - EMEA/H/C/003687/II/0056

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated study design and a protocol synopsis for study CVOT-2 (listed as a category 1 study in Annex II-D (ANX/001.7)): a multicentre, randomised, double-blind, placebo-controlled phase 4 study to assess the effect of naltrexone extended release (ER)/bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects with cardiovascular disease, as requested by CHMP in the conclusions of procedure ANX 001.6 adopted in April 2021. Annex II and the RMP (version 13) are updated accordingly

Background

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

CHMP is evaluating a type II variation for Mysimba, a centrally authorised product containing naltrexone hydrochloride/bupropion hydrochloride, to evaluate an updated study design and a protocol synopsis for study CVOT-2: a phase 4 study to assess the effect of naltrexone ER/bupropion ER on the occurrence of MACE in overweight and obese subjects with cardiovascular disease. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation.

Summary of advice

- The RMP for Mysimba (naltrexone hydrochloride/bupropion hydrochloride) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 13.0 is submitted and satisfactory responses to the request for supplementary information (RSI) are submitted.

- PRAC considered that yearly progress reports should be included in the RMP on the proposed PASS listed as a category 1 study to assess the effect of naltrexone hydrochloride/bupropion hydrochloride on the occurrence of MACE. In addition, the important identified risk of 'transient increase in blood pressure and heart rate' should be updated more thoroughly in line with the available clinical and post-marketing data, adequately reflecting relevant aspects of increases in blood pressure and heart rate, cardiac arrhythmias and hypertensive crisis as distinct entities. The MAH should propose a revised risk term that reflects the knowledge and severity of cardiovascular risks related to the medicinal product more accurately. Finally, the MAH should discuss whether it would be more appropriate to address the 'use during pregnancy' in the framework of the important potential risk of 'congenital malformations'.

5.3.4. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0061, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from study AP24534-14-203 (OPTIC) (listed as a specific obligation (SOB002) in Annex II): a randomised, open-label, phase 2 trial of ponatinib in patients with chronic myeloid leukaemia to characterise the efficacy and safety of ponatinib over a range of doses. The package leaflet and the RMP (version 21.0) are updated accordingly. The RMP (version 21.0) is updated as a response to the request for supplementary information (RSI)

Background

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

CHMP is evaluating a type II variation for Iclusig, a centrally authorised product containing ponatinib, evaluating the results from study AP24534-14-203 (OPTIC), a phase 2 study of ponatinib in patients with chronic myeloid leukaemia to characterise the efficacy and safety of ponatinib over a range of doses and proposed changed to the product information. PRAC is responsible for providing advice to CHMP on the necessary updates to the RMP to support this type II variation. For further background, see PRAC minutes January 2022.

Summary of advice

- The RMP for Iclusig (ponatinib) in the context of the variation procedure under evaluation by CHMP could be considered acceptable provided that an update to RMP version 21.1 is submitted and satisfactory responses to the RSI are submitted.
- PRAC agreed that study AP24534-14-203 (OPTIC) should be removed from the RMP as a PASS and remain as a post-authorisation efficacy study (PAES) in order to address the important identified risk of vascular occlusive events. PRAC also considered that the removal of Iclusig (ponatinib) from the additional monitoring list is acceptable.

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

None

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. Belantamab mafodotin - BLENREP (CAP) - PSUSA/00010869/202108

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Annika Folin

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 Blenrep, a centrally authorised medicine containing belantamab mafodotin and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Blenrep (belantamab mafodotin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on pneumonitis and to add it as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[13].
- In the next PSUR, the MAH should closely monitor cases of pneumonitis.

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. Desloratadine, pseudoephedrine - AERINAZE (CAP) - PSUSA/00000963/202107

Applicant: Organon N.V.

PRAC Rapporteur: Laurence de Fays

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.

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

Based on the assessment of the PSUR, PRAC reviewed the benefit-risk balance of Aerinaze, a centrally authorised medicine containing desloratadine/pseudoephedrine 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 Aerinaze (desloratadine/pseudoephedrine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add depressed mood as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should monitor the risk of suicidal ideation and discuss the need to update 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.

6.1.3. Efavirenz, emtricitabine, tenofovir – ATRIPLA[15] - PSUSA/00001201/202107

Applicant: Gilead Sciences Ireland UC

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 including responses provided by the Company in an oral explanation, PRAC reviewed the benefit-risk balance of Atripla, a medicine containing efavirenz/emtricitabine/tenofovir.

Following the submission and start of the PSUSA procedure, the European Commission (EC) adopted a decision on 15 November 2021 to withdraw the marketing authorisation(s) of Atripla (efavirenz/emtricitabine/tenofovir) due to commercial reasons. In line with the 'Guidance on handling of PSUR procedures for suspended or withdrawn / non-renewed / revoked marketing authorisations' (EMA/576230/2015) (see PRAC minutes January 2016), PRAC discussed also the need to request the submission of a further/ad-hoc PSUR.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Atripla (efavirenz/emtricitabine/tenofovir) in the approved indication(s) remains unchanged.

[14] 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.
[15] European Commission (EC) decision on the withdrawal of the marketing authorisation (MA) for Atripla dated 15 November 2021

- In the next PSUR, the Company should closely monitor cases of bone marrow oedema/lesions, osteoporosis/osteopenia/decrease in bone mineral density, the impact on diol metabolism in transgender female, as well as the safety in pregnancy and stillbirth. The Company should further monitor the potential effect of efavirenz on adrenal function in children after pre- and postnatal exposure.

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.

PRAC considered that the Company should submit to EMA, within 30 days, with the upcoming PSUR for Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) an updated comprehensive review of cases of pure red cell aplasia, including any additional data, in particular further epidemiological analyses from US and European databases together with a detailed description of the applied methodology.

6.1.4. Natalizumab - TYSABRI (CAP) - PSUSA/00002127/202108

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

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 Tysabri, a centrally authorised medicine containing natalizumab 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 Tysabri (natalizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the risk of anaemia in infants born to women exposed to natalizumab during pregnancy and the need to monitor haemoglobin levels. Therefore, the current terms of the marketing authorisation(s) should be varied[16].

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.

6.1.5. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/202108

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

[16] Update of SmPC section 4.6. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

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 Symkevi, a centrally authorised medicine containing tezacaftor/ivacaftor 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 Symkevi (tezacaftor/ivacaftor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning to raise awareness of the potential for worsening of liver function so that patients can be monitored, and timely action taken to minimise the risk of serious outcomes. Therefore, the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should provide a cumulative review of cases of seizures and discuss any potential mechanism by which tezacaftor/ivacaftor may induce seizures. The MAH should also provide a comprehensive review of cases of depression and related events, including data from literature, clinical trials and post-marketing setting. Finally, the MAH should discuss cases reporting a worsening of symptoms following initiation of treatment with tezacaftor/ivacaftor, as well as cases reported in patients without a previous history of depression.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The frequency of submission of the subsequent PSURs should be changed from 6-monthly to yearly and the list of Union reference dates (EURD list) will be updated accordingly.

6.1.6. Upadacitinib - RINVOQ (CAP) - PSUSA/00010823/202108

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

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 Rinvoq, a centrally authorised medicine containing upadacitinib and issued a recommendation on its marketing authorisation(s).

[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.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Rinvoq (upadacitinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add urinary tract infection as an undesirable effect with a frequency 'common'. Therefore, the current terms of the marketing authorisation(s) should be varied[18].

  The recommendation is without prejudice to the final conclusions of the ongoing referral procedure for Janus kinase inhibitors (JAKi) under Article 20 of Regulation (EC) No 726/2004.
- In the next PSUR, the MAH should provide a cumulative review of cases of retinal disorders, including data from clinical trials, literature and post marketing setting. The MAH should also provide a review on new data on cases of occurrence of eczema herpeticum in patients with atopic dermatitis, including a discussion on positive rechallenge/dechallenge cases.

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. (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

6.2.1. Desloratadine - AERIUS (CAP); AZOMYR (CAP); DASSELTA (CAP); DESLORATADINE ACTAVIS (CAP); DESLORATADINE RATIOPHARM (CAP); DESLORATADINE TEVA (CAP); NEOCLARITYN (CAP); NAP - PSUSA/00000962/202107

Applicants: Actavis Group PTC ehf (Desloratadine Actavis), Krka, d.d., Novo mesto (Dasselta), Organon N.V. (Aerius, Azomyr, Neoclarityn), Ratiopharm GmbH (Desloratadine ratiopharm), Teva B.V. (Desloratadine Teva), various

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Desloratadine is the active metabolite of loratadine, a long-acting histamine antagonist with selective peripheral H1-receptor antagonist activity. It is indicated for the relief of symptoms associated with allergic rhinitis and urticaria in adults, adolescents and children over the age of one year.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of Aerius, Azomyr, Dasselta, Desloratadine Actavis, Desloratadine Ratiopharm, Desloratadine Teva, Neoclarityn, centrally authorised medicines containing desloratadine, and nationally authorised medicine(s) containing desloratadine and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

[18] 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.

- Based on the review of the data on safety and efficacy, the benefit-risk balance of desloratadine-containing products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add depressed mood and eye dryness as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied[19].
- In the next PSUR, the MAH should monitor the risk of suicidal ideation and discuss the need to update the product information as warranted.

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

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

See also Annex I 16.3.

6.3.1. Amlodipine, rosuvastatin (NAP); amlodipine, perindopril, rosuvastatin (NAP) - PSUSA/00010434/202107

Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

Background

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, amlodipine a calcium channel blocker and perindopril an inhibitor of the angiotensin converting enzyme (ACE). Amlodipine/rosuvastatin and amlodipine/perindopril/rosuvastatin as fixed dose combinations (FDC) are indicated for the treatment of hypertension in patients who are estimated to have a high risk for a first cardiovascular event, for prevention of major cardiovascular events as an adjunct to correction of other risk factors or with some coincident conditions as primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. In some Member States, the FDC are authorised for the treatment of chronic stable angina pectoris and Prinzmetal angina.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing amlodipine/rosuvastatin- and amlodipine/perindopril/rosuvastatin- 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 amlodipine/rosuvastatin- and amlodipine/perindopril/rosuvastatin-containing products in the approved indication(s) remains unchanged.

[19] 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

- Nevertheless, the product information should be updated to amend the information on overdose by adding non-cardiogenic pulmonary oedema as an undesirable effect following amlodipine overdose. Therefore, the current terms of the marketing authorisation(s) should be varied[20].
- In the next PSUR, the MAHs should add myasthenia gravis as an important potential risk in the PSUR summary 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.

Additionally, PRAC agreed that the risk of non-cardiogenic pulmonary oedema is also relevant for medicinal products containing amlodipine as a mono-component or in other fixed-dose combinations. Further consideration should be given at the level of CMDh.

6.3.2. Leuprorelin[21] (NAP) - PSUSA/00010877/202107

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Leuprorelin is a gonadotropin releasing hormone (GnRH) analogue indicated for the treatment of hormone-responsive cancers such as prostate cancer and breast cancer. It may also be used for oestrogen-dependent conditions such as endometriosis or uterine fibroids. In addition, it may be used for the treatment of precocious puberty in both males and females, and to prevent premature ovulation in cycles of controlled ovarian stimulation for in vitro fertilisation (IVF).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of leuprorelin-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add idiopathic intracranial hypertension as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied[22].
- In the next PSUR, the MAH(s) of leuprorelin-containing product(s) with a paediatric indication should perform a cumulative review of cases of myalgia and discuss whether an update of the product information is warranted. In additional, the MAHs should assess the effectiveness of RMMs put in place to minimise 'medication error resulting in lack of efficacy'.

[20] Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of an opinion.
[21] Depot formulations only
[22] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to CMDh for adoption of an opinion.

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

6.3.3. Magnesium sulfate, sodium sulfate, potassium sulfate (NAP) - PSUSA/00010239/202108

Applicant(s): various

PRAC Lead: Jana Lukačišinová

Scope: Evaluation of a PSUSA procedure

Background

Magnesium sulfate, sodium sulfate, potassium sulfate are used in combination as a sulfate-based laxative for bowel cleansing prior to any medical procedure requiring a clean bowel, such as a colonoscopy or bowel surgery.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing magnesium sulfate/sodium sulfate/potassium sulfate 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 magnesium sulfate/sodium sulfate/potassium sulfate-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a detailed analysis of cases of medication errors as well as a detailed review of cases reporting cardiac arrhythmia or palpitation including cases with fatal outcome. The MAH should propose to update 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.

PRAC considered that cases of treatment with magnesium sulfate/sodium sulfate/potassium sulfate which led to a manifestation of unlisted adverse reaction(s) need to be further assessed. Further consideration is to be given at the level of CMDh.

6.3.4. Montelukast (NAP) - PSUSA/00002087/202107

Applicant(s): various

PRAC Lead: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

Background

Montelukast is a selective leukotriene receptor antagonist indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma, for the prophylaxis of asthma in which the predominant component is exercise-induced

bronchoconstriction as well as for the prophylaxis of asthma to provide symptomatic relief of seasonal allergic rhinitis. In some Member States, montelukast is also indicated for the relief of daytime and night-time symptoms of allergic rhinitis.

Based on the assessment of the PSUR(s), PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing montelukast 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 montelukast-containing product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH(s) should provide a review of any new available data on neuropsychiatric events including depression and suicidality.

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.

PRAC considered that the risk of severe and prolonged neuropsychiatric events/harms should be further assessed, and consideration should be given on existing risk minimisation measures and the need for any further ones. Further consideration is to be given at CMDh.

6.4. Follow-up to PSUR/PSUSA procedures

6.4.1. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/LEG 057

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Review of cases of abuse and dependence in patients without a history of substance disorders as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202101) adopted in September 2021

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH for Lyrica to submit an updated review of cases of abuse and dependence in patients without a history of substance disorder. For background information, see PRAC minutes September 2021[23]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation to update[24] the product information to amend the warning on misuse, abuse and dependence, as well as on

[23] Held 30 August – 02 September 2021
[24] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.

withdrawal symptoms, and to add drug dependence as an undesirable effect with a frequency 'not known'.

6.4.2. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/LEG 009

Applicant: Upjohn EESV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Review of cases of abuse and dependence in patients without a history of substance disorders as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002511/202101) adopted in September 2021

Background

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

Following the evaluation of the most recently submitted PSUR(s) for the above-mentioned medicine(s), PRAC requested the MAH for Pregabalin Pfizer (pregabalin) to submit an updated review of cases of abuse and dependence in patients without a history of substance disorder and discuss the need for an update of the product information. For background, see PRAC minutes September 2021[25]. The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 60 days, a variation to update[26] the product information to amend the warning on misuse, abuse and dependence, as well as on withdrawal symptoms, and to add drug dependence as an undesirable effect with a frequency 'not known'.

6.5. Variation procedure(s) resulting from PSUSA evaluation

None

6.6. Expedited summary safety reviews[27]

6.6.1. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) – EMEA/H/C/005737/MEA 014.8

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Ninth expedited summary safety report (SSR) for COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S, recombinant)) during the coronavirus disease (COVID-19) pandemic

Background

[25] Held 30 August – 02 September 2021
[26] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly.
[27] 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

COVID-19 vaccine (Ad26.COV2-S [recombinant]) is a monovalent vaccine composed of a recombinant, replication-incompetent human adenovirus type 26 vector that encodes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) full-length spike (S) glycoprotein indicated, as COVID-19 vaccine Janssen, a centrally authorised vaccine, for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

PRAC assessed the ninth expedited summary safety report (SSR) for the safety monitoring of COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S, recombinant)). At the plenary meeting, PRAC adopted its conclusions.

Summary of advice/conclusion(s)

- The MAH should submit to EMA, within 30 days, a variation to add cutaneous small vessel vasculitis as an undesirable effect with a frequency 'not known'.
- In the next SSR, the MAH should provide a cumulative review of cases of pericarditis and pleuro-pericarditis.
- The MAH should submit to EMA, within 45 days, a cumulative review of cases of coronary artery disease including myocardial infarction based on data from clinical trials, post-marketing data and literature, including (age) stratified observed/expected (O/E) analyses. The review should include data from ongoing epidemiological studies, including the recent EPI-PHARE[28] study.

Based on the same EPI-PHARE study, PRAC also agreed that the MAH of Vaxzevria (COVID-19 vaccine (ChAdOx1-S [recombinant]) should submit to EMA, within 45 days, a cumulative review of cases of coronary artery disease including myocardial infarction based on data from clinical trials, post-marketing data and literature, including (age) stratified observed/expected (O/E) analyses, as well as any relevant data from ongoing epidemiological studies.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[29]

See Annex I 17.1.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[30]

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)[31]

7.3.1. Direct acting antivirals (DAAV): Dasabuvir - EXVIERA (CAP); elbasvir, grazoprevir - ZEPATIER (CAP); glecaprevir, pibrentasvir - MAVIRET (CAP); ledipasvir, sofosbuvir - HARVONI (CAP); ombitasvir,

[28] Botton J, Jabagi MJ, Bertrand M, Baricault B, Drouin J, Le Vu S, Weill A, Farrington P, Zureik M, Dray-Spira R. Évaluation du risque d'infarctus du myocarde, d'accident vasculaire cérébral et d'embolie pulmonaire suite aux différents vaccins anti-COVID-19 chez les adultes de moins de 75 ans en France. EPI-PHARE, January 2022
[29] In accordance with Article 107n of Directive 2001/83/EC
[30] 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
[31] In accordance with Article 107p-q of Directive 2001/83/EC

peritepreviR, ritonavir - VIEKIRAX (CAP); sofosbuvir - SOVALDI (CAP); sofosbuvir, velpatasvir - EPCLUSA (CAP); sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/PSR/J/0038

Applicant: Gilead Science International

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Final study report for a joint non-interventional PASS of early recurrence of hepatocellular carcinoma (HCC) in patients infected with chronic hepatitis C virus (HCV) after direct-acting antiviral (DAA) therapy as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 completed in December 2016 (EMEA/H/A-20/1438)

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.

Further to the conclusions dated 2016 of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438) for direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C, the MAH(s) were required to conduct a PASS on early recurrence of hepatocellular carcinoma (HCC) in patients infected with chronic hepatitis C virus (HCV) after DAAV therapy as reflected in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' of the marketing authorisation(s). The MAHs for DAAV indicated for the treatment of hepatitis C, namely Epclusa (sofosbuvir/velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir/sofosbuvir), Maviret (glecaprevir/ pibrentasvir), Sovaldi (sofosbuvir), Viekirax (ombitasvir/peritepreviR/ritonavir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and Zepatier (elbasvir/grazoprevir), submitted to EMA the final results of the joint study entitled DAA-PASS, a prospective, observational study to estimate the risk of early HCC recurrence associated with DAAV therapy exposure relative to no DAAV therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC. The MAHs also submitted to EMA the results of a systematic review and meta-analysis as previously requested by PRAC. For background, see PRAC minutes June 2020.

PRAC discussed the final study results of the observational study. PRAC is responsible for evaluating the PASS final results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the joint PASS and the assessment from the Rapporteur, PRAC considered that the obligation to perform the PASS is fulfilled.
- Results of the DAA-PASS study together with the results of a systematic review/meta-analysis did not show an increased risk of HCC recurrence for patients treated with DAAV.
- PRAC recommended to vary the terms of the marketing authorisation(s)[32] by removing the study requirement from the conditions with regard to the safe and effective use of the medicinal products. In addition, the medicinal products should be removed from the list of medicines under additional monitoring.

[32] Update of all Annex II-D. The PRAC AR and PRAC recommendation are transmitted to CHMP for adoption of an opinion

- The MAHs should submit to EMA at the next regulatory opportunity, updated RMPs to remove 'recurrence of HCC' from the list of safety concerns as an important potential risk.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[33]

See also Annex I 17.4.

7.4.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/II/0031, Orphan

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.2, 4.4, 4.9 and 5.1 of the SmPC based on the final study report from study SNT-IV-003 (PAROS) (listed as a category 2 study in the RMP and Annex II (SOB003)): a non-interventional study of clinical experience in patients prescribed Raxone (idebenone) for the treatment of Leber's hereditary optic neuropathy (LHON). Annex II and the RMP (version 1.13) are updated accordingly

Background

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

As stated in the RMP of Raxone (idebanone) and in the condition(s) to the marketing authorisation(s) of the medicinal product (Annex II-E), the MAH submitted the results of study SNT-IV-003 (PAROS), a non-interventional study of clinical experience in patients prescribed Raxone (idebenone) for the treatment of Leber's hereditary optic neuropathy (LHON). The Rapporteur assessed the MAH's final study report.

Summary of advice

- Based on the available data and the assessment of the Rapporteur, PRAC considered that further information is necessary before the ongoing variation assessing the final study report can be recommended for approval. In addition, the RMP for Raxone (idebanone) in the context of the variation could be considered acceptable provided that an update to RMP version 1.13 is submitted.
- The MAH should clarify the proposed change in the list of safety concerns from 'use in children under 14 years of age with Leber's hereditary optic neuropathy (LHON)' to 'use in children under 12 years of age with LHON' as missing information. PRAC agreed with the removal of 'safety on long term use of Raxone' as missing information. The maintenance of other aspects of missing information is agreed, considering the scarce data gathered in the PAROS study relative to the specific population and paediatric population.

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.

[33] 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

7.5.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 044.13

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 0044.12 [third interval safety registry for study CNTO1275PSO4056: an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)] as per the request for supplementary information (RSI) adopted in November 2021

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 Stelara (ustekinumab), the MAH is requested to conduct a study entitled 'an observational PASS of ustekinumab in the treatment of paediatric patients aged 12 years and older with moderate to severe plaque psoriasis (adolescent registry)' to assess the long-term safety and long-term impact on growth and development in the paediatric patient population. An interim report for the study was assessed by the Rapporteur for PRAC review together with the MAH's responses to the requests for supplementary information (RSI). For further background, see PRAC minutes November 2021[34].

Summary of advice

- Based on the available data and the Rapporteur's review, PRAC agreed that the PASS protocol can be amended to remove the requirement for routine annual Tanner staging. Nonetheless, given that the study is conducted in routine clinical practice, it is expected that, as clinically appropriate, physicians involved in the study would perform Tanner staging, thus adverse events and serious adverse events including any events that might involve effects of ustekinumab on development, should continue to be reported. 'Long-term impact on growth and development in paediatric psoriasis patients 6 years and older' should be retained as missing information in the RMP.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

[34] Held 25-28 October 2021

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

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

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

8.1. Annual reassessments of the marketing authorisation

See also Annex I 18.1.

8.1.1. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/S/0029 (with RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

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.

Raxone, a centrally authorised product containing idebenone, was authorised in 2015 under exceptional circumstances.

The benefit-risk of Raxone 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 obligation(s) and safety data submitted together with the Rapporteurs' assessment report, PRAC considered that the annual re-assessment procedure could be finalised for Raxone (idebanone) if satisfactory clarification is given on some pending issues. These include amendments to RMP version 1.13 related to study SNT-IV-005 (LEROS)[35]. The MAH should clarify the proposed change in the list of safety concerns from 'use in children under 14 years of age with Leber's hereditary optic neuropathy (LHON)' to 'use in children under 12 years of age with LHON' as missing information.

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.

[35] An open-label study to assess the efficacy and safety of Raxone in LHON patients

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 Chair welcomed Marie Louise Schougaard Christiansen as the new alternate for Denmark. The Chair also announced that Laurence de Fays was to step down from PRAC as the alternate for Belgium following the current meeting. The Chair thanked her for her contribution to PRAC.

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

12.3.1. EMA Emergency task force (ETF) - PRAC nominations

PRAC noted that the following PRAC members were appointed as PRAC representatives in the EMA Emergency task force (ETF): Jean-Michel Dogné, Ulla Wändel Liminga and Daniel Morales.

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 ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance.

12.5. Cooperation with International Regulators

12.5.1. International Conference on Harmonisation (ICH) E2D(R1) - Post-approval safety data management: definitions and standards for expedited reporting

The EMA Secretariat presented to PRAC a summary of the activities related to the ongoing revision of ICH E2D(R1) guideline on 'post-approval safety data management: definitions and standards for expedited reporting', including the next steps and timelines for adoption foreseen in 2024. PRAC was also informed that Željana Margan Koletić had been appointed as PRAC liaison on ICH E2D(R1) activities.

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

None

12.7. PRAC work plan

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

None

12.10.3. PSURs repository

None

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

PRAC endorsed the draft revised EURD list, version March 2022, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting of March 2022, the updated EURD list was

adopted by CHMP and CMDh at their March 2022 meetings and published on the EMA website, see: Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> 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 signal management review technical (SMART) working group meeting on Methods held on 21 February 2022, including further information on the SMART methods workplan for 2022-2025, together with an update on the ongoing activities. It was also announced that a new Chair of the SMART Methods WG will be appointed.

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 of 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 accordingly, see: Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. EudraVigilance – annual report 2021

The EMA secretariat presented to PRAC the 2021 EudraVigilance annual report for the European Parliament, the Council and the Commission in line with Article 24(2), paragraph 2 of Regulation (EC) No. 726/2004. Following the EMA Management Board meeting, the report will be submitted to the EU institutions and published on the EMA website.

Post-meeting note: On 17 March 2022, the EudraVigilance annual report 2021 (EMA/719826/2021) was published on the EMA website.

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Impact of pharmacovigilance activities

None

12.21. Others

12.21.1. Data analysis and real-world interrogation network (DARWIN EU) – introduction of the coordination centre and next steps for real-world evidence (RWE)

The EMA Secretariat presented to PRAC an introduction to the 'Data Analysis and Real World Interrogation Network (DARWIN EU)', the establishment of the DARWIN EU coordination centre since February 2022, the aim of the project as well as the implementation roadmap. The EMA Secretariat also gave an overview of the ongoing real world evidence (RWE) studies with PRAC. Further update will be given mid-2022.

12.21.2. Data protection notice – processing of scientific Committees (CxMP) members/alternates' contact details

Following the removal of the PRAC members/alternates personal data from the EMA website, the Committee was informed of a data protection notice (DPN) that will allow sharing scientific committees' members/alternates' contact details within the network.

Post-meeting note: On 10 March 2022, the DPN was published on the EMA website: European Medicines Agency's Data Protection Notice - For the processing of the contact points of scientific committees (CXMP) members/alternates' for internal use by the same committees (europa.eu)

12.21.3. Pharmacovigilance business team - activities and work plan

The EMA Secretariat presented to PRAC the 'Pharmacovigilance business team mandate' aiming at supporting PRAC on pharmacovigilance legislation implementation issues in the area of EudraVigilance and on key operational topics requiring detailed discussion among EU regulatory network. An overview of the 2021 activities was provided, mainly related to COVID-19 pandemic and individual case safety reports (ICSR) reporting. The EMA Secretariat also presented to PRAC the workplan for 2022.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[36]

14.1. New signals detected from EU spontaneous reporting systems

None

[36] 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.

14.2. New signals detected from other sources

14.2.1. Pneumococcal polysaccharide vaccine (23 serotypes) (NAP)

Applicant(s): various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of extensive swelling of vaccinated limb

EPITT 19768 – New signal

Lead Member State(s): DE

14.2.2. Tocilizumab - ROACTEMRA (CAP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of pancreatitis

EPITT 19777 – New signal

Lead Member State(s): DE

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 below-mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Doxorubicin hydrochloride - - EMEA/H/C/005330

Scope: Treatment of breast cancer, ovarian cancer, multiple myeloma, and acquired immunodeficiency syndrome (AIDS) related Kaposi's sarcoma

15.1.2. Ertapenem - - EMEA/H/C/005815

Scope: Treatment of bacterial infections and prophylaxis of surgical site infection following elective colorectal surgery

15.1.3. Ganirelix - - EMEA/H/C/005641

Scope: Prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART)

15.1.4. Sitagliptin, metformin hydrochloride - - EMEA/H/C/005850

Scope: Treatment of type 2 diabetes mellitus

15.1.5. Sugammadex - - EMEA/H/C/005760

Scope: Reversal of neuromuscular blockade induced by rocuronium or vecuronium

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 below-mentioned medicine(s).

15.2.1. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/WS2210/0076; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS2210/0100; dolutegravir, lamivudine - DOVATO (CAP) - EMEA/H/C/004909/WS2210/0028; dolutegravir, rilpivirine - JULUCA (CAP) - EMEA/H/C/004427/WS2210/0041

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: Submisson of updated RMPs for Tivicay (dolutegravir - RMP version 17), Triumeq (dolutegravir/abacavir/lamivudine – RMP version 18), Dovato (dolutegravir/lamivudine – RMP version 2) and Juluca (dolutegravir/rilpivirine – RMP version 3) following the completion of worksharing variation WS1810 finalised in January 2021 that assessed the final report for study 201177 (EuroSIDA) (listed as a category 3 study in the RMP): a prospective observational cohort study on clinical and virological outcome of European patients infected with human immunodeficiency virus (HIV). In addition, the MAH took the opportunity to propose a harmonisation of the risks across all 4 dolutegravir-containing product RMPs and other minor updates (including study details and epidemiology data)

15.2.2. Duloxetine - DULOXETINE MYLAN (CAP), NAP - EMEA/H/C/003981/WS2214/0029

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of an updated RMP (version 5.0) in order to align the RMP with that of the originator duloxetine-containing product. The MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and to achieve one RMP covering multiple different marketing authorisations containing the same active substance for which the MAH has an approved RMP. The RMP is also updated with the results of a follow-up questionnaire pertaining to suicidality as recommended in renewal procedure (R/0021) finalised in December 2019

15.2.3. Fentanyl - EFFENTORA (CAP), NAP - EMEA/H/C/000833/WS2212/0060

Applicant: Teva B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 5.1) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and to implement PRAC requests arising from previous assessments as follows: 1) revision of the list of safety concerns; 2) update of the key messages of the educational materials in line with another centrally authorised product containing fentanyl. As a result, Annex II on additional risk minimisation measures

is updated accordingly

15.2.4. Fentanyl - PECFENT (CAP) - EMEA/H/C/001164/II/0054

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 7.1) in line with the outcome of the last PSUR single assessment (PSUSA) procedure (PSUSA 00001369/202004) finalised in January 2021 in order to update the key messages of the educational materials in line with another centrally authorised product containing fentanyl. As a result, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. Finally, the MAH took the opportunity to bring the RMP in line with revision 2 of GVP module V on 'Risk management systems' and the product information in line with the latest quality review of documents (QRD) template (version 10.2)

15.2.5. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/II/0026, Orphan

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 3.1) to remove carcinogenicity in rats as missing information and to add a targeted questionnaire as routine pharmacovigilance measure and a patient alert card as additional risk minimisation for liver transplant rejection. In addition, the RMP is updated to add 'injection site reactions' and 'immunogenicity' as risks not considered important for inclusion in the list of safety concerns (S.VII.1.1) and to update the patient alert card with additional warnings on hepatic monitoring and ocular toxicity. The MAH took the opportunity to include further minor updates to the RMP

15.2.6. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0037

Applicant: Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of an updated RMP (version 9.0) to update the list of safety concerns and to discontinue the use of targeted adverse event follow-up questionnaire (FUQ) for angioedema following the completion of variation II/0033 finalised in March 2021 that assessed the final study report for a non-interventional PASS on the evaluation of the safety profile of lurasidone: a PASS using United States administrative claims databases in order to compare the incidence of important identified risks and important potential risks in patients treated with lurasidone to patients treated with other second-generation oral atypical antipsychotics (OAAs)

15.2.7. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/II/0038

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 7.2) to remove study D3820R00009 (listed

as a category 3 study in the RMP): an observational drug utilisation PASS of Moventig (naloxegol) in selected European populations, following the completion of procedure MEA 006.11 in November 2021

15.2.8. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/II/0087

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.6) to include data from the booster/third dose, including data in patients who have undergone a solid organ transplantation, following the outcome of procedures II/0062 (third dose in immunocompromise as part of the primary vaccination) and II/0067 (booster dose) finalised in October 2021. The MAH took the opportunity to update the RMP regarding the discontinuation of enrolment in study C4591015: a phase 2/3 study to evaluate the safety, tolerability, and immunogenicity in healthy pregnant women 18 years of age and older and the final clinical study report (CSR) milestones

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 below-mentioned medicine(s).

15.3.1. Agalsidase alfa - REPLAGAL (CAP) - EMEA/H/C/000369/II/0117

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of sections 4.2 and 6.6 of the SmPC in order to add self-administration by a trained patient and/or a caregiver as a new method of administration. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information. The RMP (version 0.1) is updated accordingly

15.3.2. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0064

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include adjuvant treatment of non-small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy for adult patients whose tumours have programmed death-ligand 1 (PD-L1) expression on ≥ 1% of tumour cells (TC) for Tecentriq (atezolizumab) as monotherapy based on the results from pivotal study GO29527 (IMpower010): a phase 3, open-label, randomized study to investigate the efficacy and safety of atezolizumab compared with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of Tecentriq (atezolizumab) 840 mg concentrate for solution for infusion SmPC and Tecentriq (atezolizumab) 1,200 mg concentrate for solution for infusion SmPC are updated. The package leaflet and the RMP (version 21.0) are updated. The MAH took the opportunity to introduce minor editorial

updates throughout the product information

15.3.3. Autologous peripheral blood T cells CD[37]4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - TECARTUS (CAP) - EMEA/H/C/005102/II/0008/G, Orphan

Applicant: Kite Pharma EU B.V, ATMP[38]

PRAC Rapporteur: Menno van der Elst

Scope: Grouped variations consisting of: 1) extension of indication to include treatment of adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL); 2) change the drug product dose specification for the new indication. As a consequence, sections 2.2, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 1.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.4. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - EMEA/H/C/004449/X/0040/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Grouped application consisting of: 1) extension application to introduce a new strength 30/120/15 mg; 2) extension of indication to include a paediatric indication by adding the use in patients of 2 years of age and older and weighing at least 14 kg. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated to support the extension of indication. The RMP (version 3.1) is updated in accordance

15.3.5. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/II/0099, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC based on final results from study C25006 (listed as a category 2 study in the RMP (SOB 010)): a multicentre open-label, phase 4 study of 50 patients with relapsed/refractory systemic anaplastic large cell lymphoma (ALCL) undertaken to further evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients who had previously received at least 1 multiagent chemotherapy regimen. In addition, the MAH took the opportunity to delete SOB 010 from Annex II and to delete the mention of conditional approval from Annex II and the package leaflet. The RMP (version 16.1) is updated accordingly

[37] Cluster of differentiation
[38] Advanced therapy medicinal product

15.3.6. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/WS2150/0146; PLAVIX (CAP) - EMEA/H/C/000174/WS2150/0145; clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP) - EMEA/H/C/001143/WS2150/0060

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include clopidogrel in combination with acetylsalicylic acid in ST segment elevation acute myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The RMP (version 1.5) for Iscover/Plavix (clopidogrel) is updated accordingly. In addition, the MAH took the opportunity to introduce an editorial update in the labelling

15.3.7. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - EMEA/H/C/004282/II/0018/G, Orphan

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Grouped variations consisting of: 1) extension of indication to add treatment of relapsed/refractory acute myeloid leukaemia (AML) in paediatric patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the new safety and efficacy data from the paediatric clinical study AAML1421: a phase 1/2 study of liposomal daunorubicin/cytarabine alone followed by fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) (FLAG) for children with relapsed AML. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the product information is updated in line with the latest quality review of documents (QRD) template (version 10.2); 2) submission of the final data from paediatric clinical study CPX-MA-1201: a phase 1/pilot study of liposomal daunorubicin/cytarabine for children, adolescents and young adults with recurrent or refractory hematologic malignancies, in support of the extension of indication

15.3.8. Defibrotide - DEFITELIO (CAP) - EMEA/H/C/002393/II/0056, Orphan

Applicant: Gentium S.r.l.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study 15-007 (listed as a specific obligation in Annex II): a phase 3, randomised, adaptive study of defibrotide vs. best supportive care in the prevention of hepatic veno-occlusive disease in adult and paediatric patients undergoing hematopoietic stem cell transplant (HSCT). The RMP (version 9) is updated accordingly. The MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) (template 10.2). In addition, the MAH introduced some minor correction throughout the product information

15.3.9. Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/X/0079/G

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped applications consisting of: 1) extension application to introduce a new strength (90 mg/90 mg/120 mg/6 mg film-coated tablets); 2) extension of indication to include treatment of human immunodeficiency virus 1 (HIV 1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in paediatric patients aged from 2 years and with body weight at least 14 kg. As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to support the extended indication. The package leaflet and the RMP (version 5.1) are updated in accordance

15.3.10. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0057

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to reflect updated safety and efficacy data from the final analysis of study 9785-CCL-0335 (ARCHES): a phase 3 randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of enzalutamide plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with metastatic hormone-sensitive prostate cancer (mHSPC). The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC

15.3.11. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0010/G, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of an update of section 5.3 of the SmPC in order to update the non-clinical information based on data from: 1) study 20147822: a 6-month carcinogenicity study of fenfluramine hydrochloride in mice; 2) study 8001993: a 2-year oral gavage carcinogenicity study of fenfluramine hydrochloride in rats, together with the final reports for dose range finding studies 20147821 and 20166554 and the final report for study 2021006-Z001-01: in-vitro evaluation of potential melanin binding by fenfluramine and norfenfluramine. The RMP (version 3.1) is updated accordingly

15.3.12. Fenfluramine - FINTEPLA (CAP) - EMEA/H/C/003933/II/0011/G, Orphan

Applicant: Zogenix ROI Limited

PRAC Rapporteur: Martin Huber

Scope: Grouped variations consisting of: 1) update of section 4.2 and 5.2 of the SmPC to include the relevant information regarding patients with renal impairment following the study 1902: a pharmacokinetic study of fenfluramine hydrochloride in subjects with varying degrees of impaired and normal renal function; 2) update of section 4.4 and 4.5 of the SmPC in order to reflect the relevant information on cytochrome (CYP)1A2 or CYP2B6 or CYP2D6 inducers following study 1904: a pharmacokinetic drug-drug interaction study of fenfluramine hydrochloride with and without fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor) and rifampin (CYP2B6 inducer) in healthy subjects. The RMP (version

2.2) is updated accordingly

15.3.13. Gemtuzumab ozogamicin - MYLOTARG (CAP) - EMEA/H/C/004204/II/0024, Orphan

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC based on the final results from study B176103: a single-arm, open-label, phase 4 study evaluating the QT interval, pharmacokinetics, and safety of gemtuzumab ozogamicin as a single-agent regimen in patients with relapsed or refractory CD[39]33-positive acute myeloid leukaemia. The RMP (version 2.0) is updated in accordance. In addition, the MAH took the opportunity to introduce some editorial changes in the product information

15.3.14. Givosiran - GIVLAARI (CAP) - EMEA/H/C/004775/II/0006, Orphan

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 of the SmPC to add 'blood homocysteine increase' as a new adverse drug reaction (ADR) and update of section 4.4 of the SmPC to add a related warning. The package leaflet and the RMP (version 1.1) are updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the product information and to update the local representative details for Malta and Cyprus

15.3.15. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/II/0042

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Update of section 5.1 of the SmPC in order to update efficacy and safety information based on final results from study 3001 (listed as a category 3 study in the RMP): an open label, multicentre extension study to assess the safety and efficacy of Afstyla (lonoctocog alfa) in subjects with severe haemophilia A. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. The RMP (version 6.0) is updated accordingly

15.3.16. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/II/0025, Orphan

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Adam Przybylkowski

Scope: Proposal for an alternative study to the currently agreed protocol for study AEGR-734-002 (specific obligation SOB002): a 24-month, multicentre, open label phase 4 post-authorisation efficacy study (PAES) to evaluate the efficacy, safety and immunogenicity of daily subcutaneous metreleptin treatment in patients with partial lipodystrophy due to the challenges of implementing the existing protocol. Annex II and the RMP (version 2.1) are updated accordingly. The MAH took the opportunity to update the RMP in line with the

[39] Cluster of differenciation

outcome of previous procedures and to include editorial changes

15.3.17. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/II/0024, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Submission of the final report from study CPKC412E2301 (listed as an obligation in the Annex II): a phase 3 study to investigate the efficacy in elderly patients. A final pharmacogenomic report is also provided (in fulfilment of MEA 004). Annex II and the RMP (version 7.0) are updated accordingly

15.3.18. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/II/0030, Orphan

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on pivotal study NETTER-1: a multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase 3 study comparing treatment with Luthatera ((^{177}Lu) oxodotreotide) to octreotide long-acting release (LAR) in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours. Additionally, updates are proposed in the product information to correct some information based on currently approved data. The package leaflet and the RMP (version 2.0) are updated accordingly. The MAH took the opportunity to update the details of local representatives in the package leaflet

15.3.19. Pegcetacoplan - ASPAVELI (CAP) - EMEA/H/C/005553/II/0002, Orphan

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on final results from study APL2-302 (Pegasus) (listed as a category 3 study in the RMP): a global, phase 3, prospective, randomised, multicentre, open-label, active-comparator–controlled study in 80 subjects. The objective was to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) (in fulfilment of MEA 001). The package leaflet and the RMP (version 5.) are updated accordingly

15.3.20. Pemigatinib - PEMAZYRE (CAP) - EMEA/H/C/005266/II/0005, Orphan

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final results from study INCB054828 (FIGHT-202) (listed as a specific obligation in the Annex II (SOB/002)): a phase 2 study investigating the efficacy and safety of pemigatinib in adults with advanced/metastatic or surgically unresectable cholangiocarcinoma including fibroblast growth factor receptor 2 (FGFR2) translocations who failed previous therapy. The RMP (version 2.0) and Annex II are updated accordingly

15.3.21. Pralsetinib - GAVRETO (CAP) - EMEA/H/C/005413/II/0002/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic rearranged during transfection (RET)-mutant medullary thyroid cancer for Gavreto (pralsetinib) based on the efficacy and safety data obtained from pivotal study BO42863 (ARROW): a phase 1/2 study of the highly-selective RET inhibitor, BLU-667, in patients with thyroid cancer, non-small cell lung cancer (NSCLC) and other advanced solid tumours. 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. Furthermore, some minor changes to the product information have been implemented in line with the latest anticancer guidelines recommendations; 2) extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer for Gavreto (pralsetinib) based on the efficacy and safety data obtained from pivotal study BO42863 (ARROW). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 1.1) are updated accordingly

15.3.22. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0026

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include treatment of adult patients with generalised myasthenia gravis (gMG). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH took the opportunity to introduce minor editorial corrections throughout the SmPC and package leaflet. The MAH also requested 1 year of market protection for a new indication

15.3.23. Relugolix, estradiol, norethisterone acetate - RYEQO (CAP) - EMEA/H/C/005267/II/0006

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study MVT-601-035 (listed as a category 3 study in the RMP): an international phase 3 double-blind, placebo-controlled, randomised withdrawal study of relugolix co-administered with estradiol and norethisterone in women with heavy menstrual bleeding associated with uterine fibroids to evaluate the efficacy and safety of long-term use of this medicinal product. The RMP (version 1.0) is updated accordingly

15.3.24. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0188

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study MA28150 (RITAZAREM) (listed as an interventional category 3 study in the RMP): an international, open label, randomised controlled trial comparing rituximab with azathioprine as therapy for maintenance of remission for anti-neutrophilcytoplasm antibody (ANCA)-associated vasculitis. The RMP (version 23.0) is updated accordingly

15.3.25. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0053

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include treatment of patients with graft versus host disease (GvHD) aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8. 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives for the Netherlands in the package leaflet

15.3.26. Tisagenlecleucel - KYMRIAH (CAP) - EMEA/H/C/004090/II/0044, Orphan

Applicant: Novartis Europharm Limited, ATMP[40]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with follicular lymphoma (FL) after two or more lines of therapy who are refractory, or relapsed during or within 6 months after completion of anti-CD[41]20 antibody maintenance, or relapsed after autologous haematopoietic stem cell transplantation (HSCT). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH took the opportunity to introduce minor editorial corrections throughout the product information to bring in line with the latest quality review of documents (QRD) template (version 10.2)

15.3.27. Trastuzumab deruxtecan - ENHERTU (CAP) - EMEA/H/C/005124/II/0014

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received one or more prior anti-HER2-based regimens. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and RMP (version 1.2) are updated accordingly

15.3.28. Turoctocog alfa pegol - ESPEROCT (CAP) - EMEA/H/C/004883/II/0010, Orphan

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

[40] Advanced therapy medicinal product
[41] Cluster of differentiation

Scope: Update of sections 4.4 and 4.8 of the SmPC to add a new warning and update the list of adverse drug reactions (ADRs) based on post-marketing data concerning a lack of factor VIII activity in patients switching from a similar factor VIII product to Esperoct (turoctocog alfa pegol). The package leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information and to bring the product information in line with the latest quality review of documents (QRD) (template 10.2). The RMP (version 2.0) is updated accordingly

15.3.29. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/II/0015/G

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Grouped variation consisting of: 1) update of sections 4.8 to add neutropenia and 5.1 of the SmPC in order to update efficacy information of Rinvoq (upadacitinib) in ankylosing spondylitis (AS) patients who are biologic disease modifying anti rheumatic drug (DMARD) inadequate responders (bDMARD-IR) based on interim results from study M19-944: a phase 3, randomized, double-blind, study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with active ankylosing spondylitis (AS) who have an inadequate response (IR) to bDMARD; 2) update of section 5.1 of the SmPC in order to include long term (through week 104) data in AS patients who are naïve to previous treatment with a bDMARD based on interim results from study M16-098: a multicentre, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of upadacitinib in subjects with active AS. The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes in the product information

15.3.30. Volanesorsen - WAYLIVRA (CAP) - EMEA/H/C/004538/II/0017/G, Orphan

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.8 and 5.1 of the SmPC based on the final results from study ISIS 304801 CS7: a multicentre open label extension study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome. The package leaflet and the RMP (version 2.1) are updated accordingly. The RMP is updated: 1) to reflect a change in the distribution methodology of the educational materials and to clarify what is meant by the prescriber kit; 2) to reflect the final results from study ISIS 304801 (CS17): a phase 2/3 double blind, randomized, placebo-controlled study, with an open label extension of volanesorsen (ISIS 304801) administered subcutaneously to patients with familial partial lipodystrophy. In addition, the MAH took the opportunity to implement editorial changes to the product information in order to align with the latest quality review of documents (QRD) template and to introduce minor linguistic update to Annex III of the product information to support product launch

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 below-mentioned medicines 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. Aflibercept[42] - ZALTRAP (CAP) - PSUSA/00010019/202108

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.2. Agalsidase alfa - REPLAGAL (CAP) - PSUSA/00000069/202108

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.3. Apalutamide - ERLEADA (CAP) - PSUSA/00010745/202108

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.4. Ataluren - TRANSLARNA (CAP) - PSUSA/00010274/202107

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.5. Baloxavir marboxil - XOFLUZA (CAP) - PSUSA/00010895/202108

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

[42] Oncological indication(s) only

16.1.6. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/202108

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.7. Bempedoic acid- NILEMDO (CAP); bempedoic acid, ezetimibe - NUSTENDI (CAP) - PSUSA/00010841/202108

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.8. Bictegravir, emtricitabine, tenofovir alafenamide - BIKTARVY (CAP) - PSUSA/00010695/202108

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.9. Botulinum toxin type A - NUCEIVA (CAP) - PSUSA/00010796/202107

Applicant: Evolus Pharma B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.10. Bulevirtide - HEPCLUDEX (CAP) - PSUSA/00010873/202107

Applicant: Gilead Sciences Ireland Unlimited Company

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.11. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/202108

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.1.12. Coronavirus (COVID-19) vaccine (Ad26.COV2-S, recombinant) - COVID-19 VACCINE JANSSEN (CAP) - PSUSA/00010916/202108

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.13. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202107

Applicant: Bayer AG

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.14. Daunorubicin, cytarabine - VYXEOS LIPOSOMAL (CAP) - PSUSA/00010701/202108

Applicant: Jazz Pharmaceuticals Ireland Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.15. Defatted powder of Arachis hypogaea L., semen (peanuts) - PALFORZIA (CAP) - PSUSA/00010902/202107

Applicant: Aimmune Therapeutics Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.16. Eravacycline - XERAVA (CAP) - PSUSA/00010718/202108

Applicant: Paion Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.17. Evinacumab - EVKEEZA (CAP) - PSUSA/00010945/202108

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.18. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/202108

Applicant: Holostem Terapie Avanzate s.r.l., ATMP[43]

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.19. Fedratinib - INREBIC (CAP) - PSUSA/00010909/202108

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sonja Hrabcik

[43] Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

16.1.20. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/202108

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.21. Fostemsavir - RUKOBIA (CAP) - PSUSA/00010911/202108

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.22. Hydrocortisone[44] [45] - ALKINDI (CAP) - PSUSA/00010674/202108

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.23. Icatibant - FIRAZYR (CAP) - PSUSA/00001714/202107

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.24. Idelalisib - ZYDELIG (CAP) - PSUSA/00010303/202107

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.25. Imlifidase - IDEFIRIX (CAP) - PSUSA/00010870/202108

Applicant: Hansa Biopharma AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.26. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/00001759/202107

Applicant(s): Bayer AG (Betaferon), Novartis Europharm Limited (Extavia)

[44] Centrally authorised product(s)
[45] Indication for adrenal insufficiency in paediatric patients only

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.27. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/202108

Applicant: Takeda Pharmaceuticals International AG

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.28. Lefamulin - XENLETA (CAP) - PSUSA/00010872/202108

Applicant: Nabriva Therapeutics Ireland DAC

PRAC Rapporteur: Eva Jirsová

Scope: Evaluation of a PSUSA procedure

16.1.29. Lipegfilgrastim - LONQUEX (CAP) - PSUSA/00010111/202107

Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.30. Lomitapide - LOJUXTA (CAP) - PSUSA/00010112/202107

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.31. Maraviroc - CELSENTRI (CAP) - PSUSA/00001934/202108

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Palbociclib - IBRANCE (CAP) - PSUSA/00010544/202108

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.33. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/202108

Applicant: Secura Bio Limited

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

16.1.34. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/202108

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.35. Pioglitazone - ACTOS (CAP), GLUSTIN[46]; pioglitazone, glimepiride – TANDEMACT (CAP); pioglitazone, metformin - COMPETACT (CAP); GLUBRAVA (CAP) - PSUSA/00002417/202107

Applicants: Cheplapharm Arzneimittel GmbH (Actos, Competact, Tandemact), Takeda Pharma A/S (Glubrava, Glustin), various

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.36. Pretomanid - DOVPRELA (CAP) - PSUSA/00010863/202108

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.37. Risdiplam - EVRYSDI (CAP) - PSUSA/00010925/202108

Applicant: Roche Registration GmbH

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.38. Sacubitril, valsartan - ENTRESTO (CAP); NEPARVIS (CAP) - PSUSA/00010438/202107

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.39. Smallpox vaccine (live, modified vaccinia Ankara virus) - IMVANEX (CAP) - PSUSA/00010119/202107

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

[46] European Commission (EC) decision on the marketing authorisation (MA) cessation of Glustin dated 02 December 2021

16.1.40. Tisagenlecleucel - KYMRIAH (CAP) - PSUSA/00010702/202108

Applicant: Novartis Europharm Limited, ATMP[47]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.41. Tocofersolan - VEDROP (CAP) - PSUSA/00002981/202107

Applicant: Recordati Rare Diseases

PRAC Rapporteur: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

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

None

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

16.3.1. Alprostadil[48] (NAP) - PSUSA/00010021/202107

Applicant(s): various

PRAC Lead: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

16.3.2. Budesonide, salmeterol (NAP) - PSUSA/00010511/202107

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.3. Cefuroxime sodium[49] (NAP) - PSUSA/00010206/202105

Applicant(s): various

PRAC Lead: Krõõt Aab

Scope: Evaluation of a PSUSA procedure

16.3.4. Everolimus[50] (NAP) - PSUSA/00010269/202107

Applicant(s): various

[47] Advanced therapy medicinal product
[48] Indicated for patency of the ductus arteriosus only
[49] Intracameral use only
[50] Indicated for rejection of transplanted organs only

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.5. Fluocinolone acetonide[51] (NAP) - PSUSA/00010224/202108

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.6. Fluticasone propionate, formoterol fumarate dihydrate (NAP) - PSUSA/00010339/202107

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.3.7. Human plasma protease C1 inhibitor[52] (NAP) - PSUSA/00010163/202108

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3.8. Indium (^{111}In) chloride (NAP); indium (^{111}In) oxine (NAP) - PSUSA/00001734/202107

Applicant(s): various

PRAC Lead: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

16.3.9. Lovastatin (NAP) - PSUSA/00010051/202107

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.3.10. Pilocarpine, timolol (NAP) - PSUSA/00002408/202107

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[51] Intravitreal implant(s) in applicator only
[52] Nationally authorised product(s) only

16.3.11. Tiapride (NAP) - PSUSA/00002944/202107

Applicant(s): various

PRAC Lead: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

16.3.12. Timolol[53] (NAP) - PSUSA/00010439/202107

Applicant(s): various

PRAC Lead: Martin Huber

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. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0025

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC concerning immunogenicity and loss of efficacy due to anti-emicizumab antibodies as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010668/202011) adopted in June 2021, together with a review of haemorrhagic cases as requested in the conclusions of the PSUSA procedure (PSUSA/00010668/202005) finalised in January 2021. The RMP (version 3.0) is updated accordingly

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)[54]

17.1.1. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/PSA/S/0083

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol previously agreed in November 2013 for lomitapide observational worldwide evaluation registry to evaluate the occurrence and

[53] Indicated for eye preparations only
[54] In accordance with Article 107n of Directive 2001/83/EC

outcomes of pregnancy in females of reproductive potential treated with lomitapide

17.1.2. Valproate (NAP) - EMEA/H/N/PSP/J/0072.6

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

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to PSP/J/0072.5 [progress report for a joint retrospective observational study to investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in November 2021[55]

17.1.3. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSA/S/0081.1

Applicant: Novartis Europharm Ltd, ATMP[56]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0081 [substantial amendment to a protocol previously agreed in March 2021 (PSA/S/0066) for a post-authorisation multicentre, multinational, longitudinal, observational safety registry study to collect long-term safety information associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products] as per the request for supplementary information (RSI) adopted in January 2022

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)[57]

17.2.1. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 002

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study PS0038: a non-interventional cohort study on the safety of bimekizumab in patients with plaque psoriasis comparing the risk of safety outcomes of interest in bimekizumab exposed patients compared to patients exposed to other biologics [final clinical study report (CSR) expected in December 2023] (from initial opinion/marketing authorisation(s))

17.2.2. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 003

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study PS0036: bimekizumab pregnancy exposure and outcome registry

[55] Held 25-28 October 2021
[56] Advanced therapy medicinal product
[57] 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

- an OTIS[58] autoimmune diseases in pregnancy study (from initial opinion/marketing authorisation(s))

17.2.3. Bimekizumab - BIMZELX (CAP) - EMEA/H/C/005316/MEA 004

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for study PS0037: an observational cohort study to evaluate bimekizumab exposure during pregnancy and monitor the safety of bimekizumab use in pregnancy (from initial opinion/marketing authorisation(s))

17.2.4. Dabigatran etexilate - PRADAXA (CAP) - EMEA/H/C/000829/MEA 051.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 051 [protocol for study 1160.307: a European non-interventional cohort study based on new data collection to measure the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age - final clinical study report (CSR) expected in Q2 2025 (from X/0122/G)] as per the request for supplementary information (RSI) adopted in October 2021[59]

17.2.5. Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/MEA 011.1

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH’s response to MEA 011 [protocol for study AMY2009: a multicentre, prospective study of daratumumab-based therapy in newly diagnosed patients with light-chain (AL) amyloidosis (from variation II/0043)] as per the request for supplementary information (RSI) adopted in November 2021[60]

17.2.6. Drospirenone, estetrol - DROVELIS (CAP) - EMEA/H/C/005336/MEA 001.1

Applicant: Chemical Works of Gedeon Richter Plc. (Gedeon Richter Plc.)

PRAC Rapporteur: Martin Huber

Scope: MAH’s response to MEA 001 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE)] as per the request for supplementary information (RSI) adopted

[58] Organization of Teratology Information Specialists
[59] Held 27-30 September 2021
[60] Held 25-28 October 2021

in November 2021[61]

17.2.7. Drospirenone, estetrol - LYDISILKA (CAP) - EMEA/H/C/005382/MEA 001.1

Applicant: Estetra SRL

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 001 [protocol for an international active surveillance study (INAS-NEES): a prospective non-interventional comparative cohort observational study to characterize and compare the risks of estetrol/drospirenone with combined oral contraceptive-containing levonorgestrel (COC-LNG) in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is venous thromboembolism (VTE), specifically deep venous thrombosis (DVT) and pulmonary embolism (PE) [final study report expected in December 2029] (from initial opinion/marketing authorisation (MA))] as per the request for supplementary information (RSI) adopted in November 2021[62]

17.2.8. Fenofibrate, simvastatin - CHOLIB (CAP) - EMEA/H/C/002559/MEA 002.7

Applicant: Mylan IRE Healthcare Limited

PRAC Rapporteur: Maia Uusküla

Scope: Substantial amendment to a protocol previously agreed in September 2017 (MEA 002.6) for study NCEPPEUPASS15741 (listed as a category 3 study in the RMP): assessment of the clinical practice regarding concomitant use of fenofibrate and simvastatin both as free and fixed combination: a European PASS

17.2.9. Filgotinib - JYSELECA (CAP) - EMEA/H/C/005113/MEA 003.2

Applicant: Galapagos N.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: MAH's response to MEA 003.1 [protocol for study GS-EU-417-9047: a non-interventional PASS of filgotinib in the treatment of patients with moderate to severe active rheumatoid arthritis within the Anti-Rheumatic Treatment in Sweden (ARTIS) register [final report expected in Q2 2030]] as per the request for supplementary information (RSI) adopted in December 2021

17.2.10. Rilpivirine - REKAMBYS (CAP) - EMEA/H/C/005060/MEA 004

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Protocol for an antiretroviral pregnancy registry: an observational, exposure-registration and follow-up study to detect major teratogenic effect in pregnancies exposed to the registry anti-retroviral drugs used to treat the human immunodeficiency virus (HIV)

[61] Held 25-28 October 2021
[62] Held 25-28 October 2021

17.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771/MEA 005

Applicant: Amgen Europe B.V., ATMP[63]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Substantial amendment to a protocol previously agreed within the initial application/marketing authorisation in 2015 for study 20130193 (listed as category 3 study in the RMP): a post-marketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and healthcare providers; and long-term safety in treated patients

17.2.12. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 017.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 017 [protocol for study A3921352: an active surveillance, post-authorisation study to characterise the safety of tofacitinib in patients with moderately to severely active ulcerative colitis in the real-world setting using data from the united registries for clinical assessment and research (UR-CARE) in the European Union (EU)] as per the request for supplementary information (RSI) adopted in September 2021

17.2.13. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 017.2

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Substantial amendment to a protocol previously agreed in June 2021 for study C4591021 (previously known as vACcine Covid-19 monitoring readinESS/Vaccine monitoring Collaboration for Europe (ACCESS/VAC4EU)): an assessment of potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis after being vaccinated with COVID-19 messenger ribonucleic acid (mRNA) vaccine estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty (tozinameran) vaccination together with a statistical analysis plan (SAP)

17.2.14. Tozinameran - COMIRNATY (CAP) - EMEA/H/C/005735/MEA 037.1

Applicant: BioNTech Manufacturing GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 037 [protocol for study C4591009: a non-interventional PASS in US to assess the occurrence of safety events of interest, including myocarditis and pericarditis (from variation II/0059 finalised in October 2021)] per the request for supplementary information (RSI) adopted in November 2021

[63] Advanced therapy medicinal product

17.2.15. Tralokinumab - ADTRALZA (CAP) - EMEA/H/C/005255/MEA 001

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for a PASS of tralokinumab use in pregnancy (listed as a category 3 study in the RMP): an observational study based on electronic healthcare data (from initial opinion/marketing autorisation(s))

17.2.16. Upadacitinib - RINVOQ (CAP) - EMEA/H/C/004760/MEA 014

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Protocol for study P21-824: a study of growth and development in adolescents with atopic dermatitis who receive upadacitinib (version 1.0)

17.3. Results of PASS imposed in the marketing authorisation(s)[64]

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)[65]

17.4.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0068

Applicant: sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC based on the final results from study OBS14697 (listed as a category 3 study in the RMP): a non-interventional, retrospective drug utilisation study (DUS) that was designed to assess in Europe the effectiveness of the dosing recommendation and to describe patterns of alirocumab utilisation in real world clinical practice (in fulfilment of MEA 019.8). In addition, the MAH took the opportunity to implement editorial changes in the product information

17.4.2. Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) complementary deoxyribonucleic acid (cDNA) sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0033, Orphan

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP[66]

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report from study STRIM-001 (listed as a category 3 study in the RMP): a cross-sectional study evaluating referring healthcare providers' and parents/carers' understanding of specific risks associated with Strimvelis treatment. The RMP (version 6.1) is updated accordingly

[64] In accordance with Article 107p-q of Directive 2001/83/EC
[65] 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
[66] Advanced therapy medicinal product

17.4.3. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0075

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Submission of the final report for study A8081062 (listed as a category 3 study in the RMP): a non-interventional, descriptive study of potential sight threatening event and severe visual loss following exposure to crizotinib (in fulfilment of MEA 024)

17.4.4. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/WS2216/0052; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/WS2216/0049; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/WS2216/0064

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report for study B20-146 (listed as a category 3 study in the RMP): a non-imposed joint PASS to evaluate the risk of de novo hepatocellular carcinoma (HCC) in patients with compensated cirrhosis treated with direct-acting antivirals (DAA) for chronic hepatitis C (HCC de novo PASS)

17.4.5. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/II/0033

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report for study B20-146 (listed as a category 3 study in the RMP): a non-imposed joint PASS to evaluate the risk of de novo hepatocellular carcinoma (HCC) in patients with compensated cirrhosis treated with direct-acting antivirals (DAA) for chronic hepatitis C (HCC de novo PASS)

17.4.6. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0028

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of the final report for study BO40853 (listed as a category 3 study in the RMP): a survey to prescribers and patients/carers to evaluate awareness, knowledge and compliance to additional risk minimisation measures for Hemlibra (emicizumab). The RMP (version 4.0) is updated accordingly

17.4.7. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0105

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from study CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra (infliximab) in patients with rheumatoid arthritis (study report excluding the joint analysis of patients in the PERSIST study) (in fulfilment of MEA 007.6)

17.4.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0111

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report from study CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Remsima (infliximab) in patients with rheumatoid arthritis (study report excluding the joint analysis of patients in the PERSIST study)

17.4.9. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0047

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study I4T-MC-JVDD (listed as a category 3 study in the RMP): safety and effectiveness of ramucirumab in patients with advanced gastric cancer in the European Union (EU) and North America - a prospective observational registry (in fulfilment of MEA 001.1). The RMP (version 10.1) is updated accordingly

17.4.10. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/II/0073

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of the final report from study BMN 162-501 (KAMPER) (formerly known as EMR700773-001) (listed as a category 3 study in the RMP): an observational drug registry to assess the long-term safety in subjects treated with Kuvan (sapropterin) (in fulfilment of MEA 020). The RMP (version 15.1) is updated accordingly

17.4.11. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS2222/0077; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS2222/0104; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS2222/0064; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS2222/0054

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study B20-146 (listed as a category 3 study in the RMP): a non-imposed joint PASS to evaluate the risk of de novo hepatocellular carcinoma (HCC) in patients with compensated cirrhosis treated with direct-acting antivirals (DAA) for chronic hepatitis C (HCC de novo PASS)

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

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/ANX 010.2

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Progress report for a drug utilisation study (DUS) to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada (alemtuzumab) infusion and immune-mediated adverse reactions, as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1483) finalised in 2019

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.16

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Annual report (covering period from 04 July 2020 to 02 July 2021) on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]

17.5.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.16

Applicant: Genzyme Europe BV

PRAC Rapporteur: Nathalie Gault

Scope: Annual report (covering period from 04 July 2020 to 02 July 2021) on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status [final clinical study report expected in Q4 2021]

17.5.4. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035.3

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Second interim report for study 20180204: a registry study to evaluate the incidence and risk of hypocalcaemia in paediatric patients treated with cinacalcet with secondary hyperparathyroidism receiving maintenance dialysis within the International Pediatric Dialysis Network (IPDN) registry

17.5.5. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.13

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Eighth annual interim report for study CICL670E2422: an observational, multicentre cohort study to evaluate the long-term exposure and safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate] together with MAH's response to ANX

038.12 [seventh annual interim report for study CICL670E2422] as per the request for supplementary information (RSI) adopted in April 2021

17.5.6. Delamanid - DELTYBA (CAP) - EMEA/H/C/002552/MEA 002.5

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Fifth annual progress report for study 242-12-402 (listed as a category 3 study in the RMP): a multicentre EU-wide observational non-interventional post-authorisation study to assess the safety and drug usage of delamanid (OPC-67683) in routine medical practice in multidrug-resistant tuberculosis patients (Delamanid registry), together with MAH's response to MEA 002.3 [fourth annual progress report for study 242-12-402] as per the request for supplementary information (RSI) adopted in February 2021]

17.5.7. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.1

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Biennial interim report for study M11-001 (aHUS registry): an observational, non-interventional multicentre, multinational study to retrospectively and prospectively collect information on the long-term safety and effectiveness of eculizumab in patients with atypical hemolytic-uremic syndrome (aHUS) who have received or continue to receive eculizumab

17.5.8. Ertugliflozin - STEGLATRO (CAP) - EMEA/H/C/004315/MEA 002.3

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: First interim report for study MK8835-062: a PASS to assess the risk of diabetic ketoacidosis among type 2 diabetes mellitus patients (T2DM) treated with ertugliflozin compared to patients treated with other antihyperglycemic agents

17.5.9. Ertugliflozin, metformin hydrochloride - SEGLUROMET (CAP) - EMEA/H/C/004314/MEA 002.3

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: First interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic agents

17.5.10. Ertugliflozin, sitagliptin - STEGLUJAN (CAP) - EMEA/H/C/004313/MEA 002.3

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: First interim report for study MK-8835-062: a PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus (T2DM) patients treated with ertugliflozin compared to patients treated with other antihyperglycemic agents

17.5.11. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 027.8

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual progress report of the ENEIDA registry (study MK-8259-042): a long-term, non-interventional observational study of patients with inflammatory bowel disease (IBD) in Spain to evaluate whether the use of golimumab is associated with a risk of colectomy for intractable disease, advanced neoplasia (colorectal cancer or high grade dysplasia), and hepatosplenic T-cell lymphoma (HSTCL) in patients with ulcerative colitis (UC) as compared with alternative therapies for similar severity of disease [final clinical study report (CSR) expected: March 2023]

17.5.12. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.10

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Eighth annual interim report for study CSTI571I2201: a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Philadelphia positive (Ph+) acute lymphoblastic leukaemia (ALL) patients treated with chemotherapy + imatinib ± haematopoietic stem cell treatment (±HSCT)

17.5.13. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/MEA 133.14

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourteenth annual paediatric inflammatory bowel disease (IBD) registry (DEVELOP): a multicentre, prospective registry of pediatric patients on long-term safety and efficacy of infliximab and other therapies, safety and efficacy of variable infliximab dosing intervals, episodic therapy, monotherapy (initiated de novo or following discontinuation of concomitant immunomodulators), combined infliximab and immunomodulator therapy (azathioprine/6-mercaptopurine (AZA/6-MP) or methotrexate (MTX))

17.5.14. Inotersen - TEGSEDI (CAP) - EMEA/H/C/004782/MEA 007.2

Applicant: Akcea Therapeutics Ireland Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim report for study TEG4005: a pregnancy surveillance programme of infants and women exposed to Tegsedi (inotersen) during pregnancy

17.5.15. Ivacaftor, tezacaftor, elexacaftor - KAFTRIO (CAP) - EMEA/H/C/005269/MEA 002.3

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Martin Huber

Scope: First annual interim report for study VX20-445-120: a five year-registry based study to assess real-world effects and utilisation patterns of elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA) in patients with cystic fibrosis (CF)

17.5.16. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.9

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

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

17.5.17. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.12

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA 006.11 [interim progress report for study D3820R00009 (EUPAS12669): an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically] as per the request for supplementary information (RSI) adopted in November 2021

17.5.18. Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.13

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Interim progress report for study D3820R00009 (EUPAS12669): an observational PASS of Moventig (naloxegol) among patients aged 18 years and older treated with opioids chronically

17.5.19. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Interim report for study 20170701: an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card (PAC) and to measure medication errors related to the use of the On-Body injector (OBI) to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC and to estimate the proportion of OBI administrations associated with medication error [final study report expected in March 2022]

17.5.20. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003.3

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interim report for study 165-501: a multicentre, prospective global observational study to evaluate the long-term safety of subcutaneous injections of Palynziq (pegvaliase (in patients with phenylketonuria

17.5.21. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005.2

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: First interim report for study 165-504: a prospective global multicentre observational safety surveillance study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding

17.5.22. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[67]) - EMEA/H/W/002300/MEA 003.6

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Fifth annual progress report for study EPI-MAL-003 (listed as a category 3 study in the RMP): a phase 4 prospective observational study to evaluate the safety, effectiveness and impact of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) in young children in sub-Saharan Africa in order to estimate the incidence of potential adverse events of special interest (AESI) and other adverse events leading to hospitalisation or death, in children vaccinated with the vaccine [final study report expected Q2 2026]

17.5.23. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.4

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Annual interim report for study VX17-661-117 (study 117) (listed as a category 3 study in the RMP): an observational cohort study on utilisation patterns and real-world effects of tezacaftor and ivacaftor combination therapy (TEZ/IVA) in patients with cystic fibrosis (CF) [final report expected in December 2023]

17.5.24. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003.4

Applicant: Almirall S.A

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual progress report 2021 for study M-14745-40: a European psoriasis registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical practice

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

17.6. Others

17.6.1. Acalabrutinib - CALQUENCE (CAP) - EMEA/H/C/005299/MEA 002.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Željana Margan Koletić

Scope: Interim report for study D8220C00008 (ASSURE): a phase 3b, multicentre, open-label, single-arm study of acalabrutinib (ACP-196) in subjects with chronic lymphocytic leukaemia to address missing information around moderate to severe cardiac impaired patients

17.6.2. Darvadstrocel - ALOFISEL (CAP) - EMEA/H/C/004258/MEA 007

Applicant: Takeda Pharma A/S, ATMP[68]

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Interim report for study Cx601-0303 (ADMIRE CDII) to evaluate the long-term safety and efficacy of darvadstrocel including adverse events of special interest (related to MEA 002)

17.6.3. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038.4

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Tiphaine Vaillant

Scope: Second interim report for open-label extension phase study CFTY720D2311: a two-year, double-blind, randomized, multicentre, active-controlled core phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a intramuscular (IM) once weekly in paediatric patients with multiple sclerosis with five-year fingolimod extension phase

17.6.4. Human C1-esterase inhibitor - CINRYZE (CAP) - EMEA/H/C/001207/MEA 021

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Proposal for discontinuation of icatibant outcome survey (IOS) study: a prospective, international, observational open-ended disease registry designed to document over time the routine clinical outcomes of adult and paediatric patients with hereditary angioedema (HAE; HAE types I and II and HAE with normal C1-esterase inhibitor), angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema, non-histaminergic idiopathic angioedema, and acquired angioedema; and notification of change to the legal entity sponsoring the study

17.6.5. Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/MEA 032.1

Applicant: Astellas Pharma Europe B.V.

[68] Advanced therapy medicinal product

PRAC Rapporteur: Ronan Grimes

Scope: MAH's response to MEA 032 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in October 2021

17.6.6. Tacrolimus - MODIGRAF (CAP) - EMEA/H/C/000954/MEA 024.1

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 024 [submission of a critical analysis of the feasibility of using alternative data sources to complement the Transplantation Pregnancy Registry International (TPRI) study outcomes on pregnancy and breastfeeding] as per the request for supplementary information (RSI) adopted in October 2021

17.6.7. Tralokinumab - ADTRALZA (CAP) - EMEA/H/C/005255/MEA 002

Applicant: LEO Pharma A/S

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study LP0162-1337 (ECZTEND) (listed as a category 3 study in the RMP): a phase 3 open label, single-arm, multicentre, long term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials (from initial opinion/marketing authorisation(s))

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 below-listed medicines 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. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0042 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sofia Trantza

Scope: Annual reassessment of the marketing authorisation

18.1.2. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0076 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Tiphaine Vaillant

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0029 (without RMP)

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.2. Entrectinib - ROZLYTREK (CAP) - EMEA/H/C/004936/R/0007 (with RMP)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.2.3. Onasemnogene abeparvovec - ZOLGENSMA (CAP) - EMEA/H/C/004750/R/0021 (without RMP)

Applicant: Novartis Gene Therapies EU Limited, ATMP[69]

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

18.2.4. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/R/0031 (without RMP)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Conditional renewal of the marketing authorisation

[69] Advanced therapy medicinal product

18.2.5. Selinexor - NEXPOVIO (CAP) - EMEA/H/C/005127/R/0005 (without RMP)

Applicant: Karyopharm Europe GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/R/0040 (without RMP)

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.2. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL MYLAN (CAP) - EMEA/H/C/004240/R/0019 (without RMP)

Applicant: Mylan Pharmaceuticals Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Efavirenz, emtricitabine, tenofovir disoproxil - EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL ZENTIVA (CAP) - EMEA/H/C/004250/R/0025 (without RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.4. Lutetium (^{177}Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/R/0032 (without RMP)

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.5. Midostaurin - RYDAPT (CAP) - EMEA/H/C/004095/R/0023 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: 5-year renewal of the marketing authorisation

18.3.6. Tivozanib - FOTIVDA (CAP) - EMEA/H/C/004131/R/0021 (without RMP)

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

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 07-10 March 2022 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Elena Kaisis	Member	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czechia	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Marie Louise Schougaard Christiansen	Alternate (Mandate as alternate for Denmark started on 01/03/2022)	Denmark	No interests declared	Full involvement
Krõõt Aab	Alternate	Estonia	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Tiphaine Vaillant	Member	France	No interests declared	Full involvement
Nathalie Gault	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Sofia Trantza	Member	Greece	No interest declared	Full involvement
Georgia Gkegka	Alternate	Greece	No interest declared	Full involvement
Julia Pallos	Member (Mandate as member for Hungary started on 11/02/2022)	Hungary	No restrictions applicable to this meeting	Full involvement
Melinda Palfi	Alternate - (Mandate as alternate for Hungary started on 11/02/2022)	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	17.2.11. Talimogene laherparepvec - IMLYGIC (CAP) - EMEA/H/C/002771 /MEA 005 17.5.4. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570 /MEA 035.317.5.19. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420 /MEA 059.2
Rhea Fitzgerald	Member	Ireland	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Anne-Cécile Vuillemin	Alternate	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member (CHMP member)	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	16.1.13. Darolutamide - NUBEQA (CAP) - PSUSA/00010843/202107 16.1.26. Interferon beta-1b - BETAFERON (CAP); EXTAVIA (CAP) - PSUSA/00001759/202107
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Sofia Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Sofia Sanches de Castro Lopes Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Dondera	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marek Juracka	Member	Slovakia	No interests declared	Full involvement
Anna Mareková	Alternate	Slovakia	No interests declared	Full involvement
Polona Golmajer	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Annalisa Capuano	Member	Independent scientific expert	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No interests declared	Full involvement
Maria Teresa Herdeiro	Member	Independent scientific expert	No interests declared	Full involvement
Patricia McGettigan	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Christelle Bizimungu	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Jo Robays	Expert - via Webex*	Belgium	No restrictions applicable to this meeting	Full involvement
Charlotte Selvais	Expert - via Webex*	Belgium	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Françoise Wuillaume	Expert - via Webex*	Belgium	No interests declared	Full involvement
Melita Dumančić	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić	Expert - via Webex*	Croatia	No restrictions applicable to this meeting	Full involvement
Petra Kaftanová	Expert - via Webex*	Czechia	No interests declared	Full involvement
Alexander Braathen	Expert - via Webex*	Denmark	No interests declared	Full involvement
Karin Erneholm	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Kristina Laursen	Expert - via Webex*	Denmark	No interests declared	Full involvement
Emma Stadsbjerg	Expert - via Webex*	Denmark	No interests declared	Full involvement
Josiane Uwera	Expert - via Webex*	Denmark	No restrictions applicable to this meeting	Full involvement
Samuel Crommelynck	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Vincent Gazin	Expert - via Webex*	France	No interests declared	Full involvement
Leo Lambart	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Marie-Caroline Pesquidous	Expert - via Webex*	France	No restrictions applicable to this meeting	Full involvement
Youssef Shaim	Expert - via Webex*	France	No restrictions	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			applicable to this meeting	
Roberto Frontini	Expert - via Webex*	Germany	No restrictions applicable to the meeting	Full involvement
Jelena Katic	Expert - via Webex*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - via Webex*	Germany	No restrictions applicable to this meeting	Full involvement
Ruchika Sharma	Expert - via Webex*	Ireland	No restrictions applicable to this meeting	Full involvement
Amanda Camilleri	Expert - via Webex*	Malta	No interests declared	Full involvement
Michal Pirozynski	Expert - via Webex*	Malta	No restrictions applicable to this meeting	Full involvement
Paul ten Berg	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Anja van Haren	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Justine Van Tongeren	Expert - via Webex*	Netherlands	No interests declared	Full involvement
Sophia Venzke	Expert – via Webex*	Netherlands	No interests declared	Full involvement
Fernanda Inês Carvalho Pereira Ribeiro Vaz	Expert – via Webex*	Portugal	No interests declared	Full involvement
Carla Torre	Expert – via Webex*	Portugal	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert – via Webex*	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:
Home>Committees>PRAC>Agendas, minutes and highlights

21. Explanatory notes

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

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

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action

may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

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

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

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

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

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

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

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

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