2 September 2016
EMA/PRAC/632773/2016
Procedure Management and Committees Support Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the PRAC meeting on 04-08 July 2016

Chair: June Raine – Vice-Chair: Almath Spooner

Health and safety information

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

Disclaimers

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

Of note, this agenda is a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction 12

1.1. Welcome and declarations of interest of members, alternates and experts 12

1.2. Agenda of the meeting of 04-08 July 2016 12

1.3. Minutes of the previous meeting on 06-09 June 2016 12

2. EU referral procedures for safety reasons: urgent EU procedures 12

2.1. Newly triggered procedures 12

2.2. Ongoing procedures 12

2.3. Procedures for finalisation 13

2.4. Planned public hearings 13

3. EU referral procedures for safety reasons: other EU referral procedures 13

3.1. Newly triggered procedures 13

3.1.1. Paracetamol (NAP) (modified release formulation) - EMEA/H/A-31/1445 13

3.1.2. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446 14

3.1.3. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP) - EMEA/H/A-31/1448 15

3.2. Ongoing procedures 16

3.2.1. Direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free): daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/A-20/1438 16

3.2.2. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - EMEA/H/A-31/1437 16

3.2.3. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: Canaglifozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapaglifozin – EDISTRIDE (CAP), FORXIGA (CAP); dapaglifozin, metformin – XIGDUO (CAP), EBYMECT (CAP); empaglifozin – JARDIANCE (CAP); empaglifozin, metformin – SYNJARDI (CAP) - EMEA/H/A-20/1442 17

3.3. Procedures for finalisation 18

3.3.1. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439 18

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request 19

3.5. Others 19

4. Signals assessment and prioritisation 20

4.1. New signals detected from EU spontaneous reporting systems 20

4.1.1. Acenocoumarol (NAP), fluindione (NAP), phenindione (NAP), phenprocoumon (NAP) 20

4.1.2. Ceftriaxone (NAP) 21

4.1.3. Loperamide (NAP) 21

4.1.4. Vildagliptin – GALVUS (CAP), JALRA (CAP), XILIARX (CAP); vildagliptin, metformin – EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP) 22

4.2. New signals detected from other sources 23

4.2.1. Fluoroquinolones (systemic use): Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin (NAP); lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 23

4.2.2. Human coagulation(plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY; simoctocog alfa – NUWIQ (CAP); turoctocog alfa – NOVOEIGHT (CAP) 24

4.2.3. Methylphenidate (NAP) 25

4.3. Signals follow-up and prioritisation 26

4.3.1. Ferrous sulfate (NAP) 26

4.3.2. Human albumin solutions (NAP) 27

4.3.3. Proton pump inhibitors (PPIs): Dexlanzoprazole (NAP), esomeprazole – NEXIUM CONTROL (CAP), NAP; lansoprazole (NAP); omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/015, PANTECTA CONTROL (CAP) - EMEA/H/C/001099/SDA/015, PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/014, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/015, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/020, NAP; rabeprazole (NAP) 28

4.3.4. Tramadol, paracetamol (NAP) 28

5. Risk management plans (RMPs) 29

5.1. Medicines in the pre-authorisation phase 29

5.1.1. Bezlotoxumab - EMEA/H/C/004136 29

5.1.2. Dasabuvir, ombitasvir, paritaprevir, ritonavir - EMEA/H/C/004235 29

5.1.3. Edotreotide - EMEA/H/C/004140, Orphan 29

5.1.4. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue - EMEA/H/C/004258, Orphan 30

5.1.5. Follitropin delta - EMEA/H/C/003994 30

5.1.6. Human immunoglobulin (Ig)G1 monoclonal antibody specific for human interleukin-1 alpha - EMEA/H/C/004388 30

5.1.7. Obeticholic acid - EMEA/H/C/004093, Orphan 30

5.1.8. Pegfilgrastim - EMEA/H/C/004342; EMEA/H/C/004023 30

5.1.9. Venetoclax - EMEA/H/C/004106, Orphan 30

5.2. Medicines in the post-authorisation phase – PRAC-led procedures 30

5.2.1. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0103 30
5.3. Medicines in the post-authorisation phase – CHMP-led procedures 31
5.3.1. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0126 31
6. Periodic safety update reports (PSURs) 32
6.1. PSUR procedures including centrally authorised products (CAPs) only 32
6.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201512 32
6.1.2. Bimatoprost, timolol - GANFORT (CAP) - PSUSA/00002961/201511 (with RMP) 33
6.1.3. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201512 (with RMP) 33
6.1.4. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201512 34
6.1.5. Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201512 35
6.1.6. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/201512 36
6.1.7. Omalizumab - XOLAIR (CAP) - PSUSA/00002214/201512 37
6.1.8. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201512 37
6.1.9. Umeclidinium bromide, vilanterol - ANORO (CAP); LAVENTAIR (CAP) - PSUSA/00010264/201512 39
6.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) 39
6.2.1. Bosentan - STAYVEER (CAP); TRACLEER (CAP); NAP - PSUSA/00000425/201511 39
6.3. PSUR procedures including nationally authorised products (NAPs) only 40
6.3.1. Apomorphine (NAP) - PSUSA/00000227/201511 40
6.3.2. Benazepril (NAP) - PSUSA/00000313/201511 42
6.3.3. Benzydamine (NAP) - PSUSA/00000375/201510 42
6.3.4. Dextromethorphan (NAP) - PSUSA/00001009/201511 43
6.3.5. Furosemide, spironolactone (NAP) - PSUSA/00001493/201512 44
6.3.6. Minoxidil (topical formulation) (NAP) - PSUSA/00002067/201510 45
6.3.7. Technetium (^{99m}Tc) mebrofenin (NAP) - PSUSA/00002861/201511 46
6.4. Follow-up to PSUR/PSUSA procedures 46
6.4.1. Ingenol mebutate - PICATO (CAP) - EMEA/H/C/002275/LEG 008 46
7. Post-authorisation safety studies (PASS) 47
7.1. Protocols of PASS imposed in the marketing authorisation(s) 47
7.1.1. Eliglustat - CERDELGA (CAP) - EMEA/H/C/PSP/0047 47
7.1.2. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/PSP/0048 48
7.1.3. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSP/0049 49
7.2. Protocols of PASS non-imposed in the marketing authorisation(s) 49
7.2.1. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 005.3 49
7.3. Results of PASS imposed in the marketing authorisation(s) 50
7.3.1. Cyproterone, ethinylestradiol (NAP) – EMEA/H/N/PSR/J/005 50
7.4. Results of PASS non-imposed in the marketing authorisation(s) 50

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation 50
7.6. Others 50
7.7. New Scientific Advice 51
7.8. Ongoing Scientific Advice 51
7.9. Final Scientific Advice (Reports and Scientific Advice letters) 51
8. Renewals of the marketing authorisation, conditional renewal and annual reassessments 51
8.1. Annual reassessments of the marketing authorisation 51
8.2. Conditional renewals of the marketing authorisation 51
8.3. Renewals of the marketing authorisation 51
9. Product related pharmacovigilance inspections 51
9.1. List of planned pharmacovigilance inspections 51
9.2. Ongoing or concluded pharmacovigilance inspections 51
9.3. Others 51
10. Other safety issues for discussion requested by the CHMP or EMA 52
10.1. Safety related variations of the marketing authorisation 52
10.2. Timing and message content in relation to Member States' safety announcements 52
10.3. Other requests 52
10.3.1. Dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/LEG 001.1; FORXIGA (CAP) - EMEA/H/C/002322/LEG 019.1 dapagliflozin, metformin – EBYMECT (CAP) - EMEA/H/C/004162/LEG 001.1; XIGDUO (CAP) - EMEA/H/C/002672/LEG 005.1 52
10.3.2. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/LEG 006 empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/LEG 004 53
10.4. Scientific Advice 53
11. Other safety issues for discussion requested by the Member States 53
11.1. Safety related variations of the marketing authorisation 53
11.2. Other requests 54
11.2.1. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP) 54
12. Organisational, regulatory and methodological matters 55
12.1. Mandate and organisation of the PRAC 55
12.2. Coordination with EMA Scientific Committees or CMDh 55
12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups 55
12.3.1. CHMP guideline on influenza vaccines 55
12.3.2. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP) - revision 55
12.3.3. Scientific Advice Working Party (SAWP) – consultation procedure: criteria 56

12.4. Cooperation within the EU regulatory network 56
12.4.1. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) 56
12.5. Cooperation with International Regulators 56
12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee 56
12.7. PRAC work plan 56
12.7.1. 2016 PRAC work plan – status update 56
12.8. Planning and reporting 57
12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions 57
12.8.2. Marketing Authorisation Applications - planned for the remainder of 2016 57
12.9. Pharmacovigilance audits and inspections 57
12.9.1. Pharmacovigilance systems and their quality systems 57
12.9.2. Pharmacovigilance inspections 57
12.9.3. Pharmacovigilance audits 57
12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list 57
12.10.1. Periodic safety update reports 57
12.10.2. Granularity and Periodicity Advisory Group (GPAG) 57
12.10.3. PSURs repository 57
12.10.4. Union reference date list – consultation on the draft list 58
12.11. Signal management 58
12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group 58
12.12. Adverse drug reactions reporting and additional reporting 58
12.12.1. Management and reporting of adverse reactions to medicinal products 58
12.12.2. Additional monitoring 58
12.12.3. List of products under additional monitoring – consultation on the draft list 58
12.13. EudraVigilance database 59
12.13.1. Activities related to the confirmation of full functionality 59
12.14. Risk management plans and effectiveness of risk minimisations 59
12.14.1. Risk management systems 59
12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations 59
12.15. Post-authorisation safety studies (PASS) 59
12.15.1. Post-authorisation Safety Studies – imposed PASS 59
12.15.2. Post-authorisation Safety Studies – non-imposed PASS 59
12.16. Community procedures 59
12.16.1. Referral procedures for safety reasons 59
12.17. Renewals, conditional renewals, annual reassessments 59
12.18. Risk communication and transparency 59

12.18.1. Public hearings – Dry run 59
12.18.2. Safety communication 60
12.19. Continuous pharmacovigilance 60
12.19.1. Incident management 60
12.19.2. Withdrawn products - Update on the handling of notifications 60
12.20. Others 60
12.20.1. Effects tables in selected important benefit/risk reviews - Pilot phase 60
12.20.2. EMA hosted industry platform on the operation of the EU pharmacovigilance legislation - Report from quarterly meeting on 01 July 2016 60
12.20.3. Strategy on measuring the impact of pharmacovigilance - draft reflection paper on PRAC criteria to prioritise collaborative impact research 61
12.20.4. Type II variations - procedural timetables 61
13. Any other business 61
14. Annex I – Signals assessment and prioritisation 61
14.1. New signals detected from EU spontaneous reporting systems 61
14.1.1. Aripiprazole – ABILIFY (CAP), ABILIFY MAINTENA (CAP) 61
14.1.2. Ipilimumab – YERVOY (CAP) 62
14.2. New signals detected from other sources 62
14.2.1. Exenatide – BYETTA (CAP), BYDUREON (CAP) 62
15. Annex I – Risk management plans 62
15.1. Medicines in the pre-authorisation phase 62
15.1.1. Enoxaparin sodium - EMEA/H/C/004264; EMEA/H/C/003795 62
15.1.2. Ivabradine - EMEA/H/C/004117 62
15.1.3. Parathyroid hormone - EMEA/H/C/003861, Orphan 62
15.1.4. Sildenafil - EMEA/H/C/004186 63
15.2. Medicines in the post-authorisation phase – PRAC-led procedure 63
15.2.1. Abacavir - ZIAGEN(CAP) - EMEA/H/C/000252/WS0956/0097/G; abacavir, lamivudine - KIVEXA(CAP) - EMEA/H/C/000581/WS0956/0070/G; abacavir, lamivudine, zidovudine - TRIZIVIR(CAP) - EMEA/H/C/000338/WS0956/0102/G; 63
15.2.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0026 63
15.2.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0026/G 63
15.2.4. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0039 64
15.2.5. Ibandronic acid – BONDRONAT (CAP) - EMEA/H/C/000101/WS0942/0074; BONVIVA (CAP) - EMEA/H/C/000501/WS0942/0056 64
15.2.6. Naltrexone, bupropion - MYSIMBA (CAP) - EMEA/H/C/003687/II/0005/G 64
15.2.7. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0083 64
15.2.8. Retigabine - TROBALT (CAP) - EMEA/H/C/001245/II/0044 64
15.3. Medicines in the post-authorisation phase – CHMP-led procedure 65
15.3.1. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/II/0020 65

15.3.2. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS0948/0096; abacavir, lamivudine – KIVEXA (CAP) - EMEA/H/C/000581/WS0948/0069; abacavir, dolutegravir, lamivudine – TRIUMEQ (CAP) - EMEA/H/C/002754/WS0948/0027; 65
15.3.3. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0097 65
15.3.4. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0006/G 65
15.3.5. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0039 66
15.3.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0012 66
15.3.7. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0013 66
15.3.8. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0032 66
15.3.9. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0035/G 66
15.3.10. Empagliflozin - JARDIANCE(CAP) - EMEA/H/C/002677/WS0926/0017; empagliflozin, metformin - SYNJARDY(CAP) - EMEA/H/C/003770/WS0926/0016 67
15.3.11. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/X/0029 67
15.3.12. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/II/0053 67
15.3.13. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/X/0050/G 67
15.3.14. Fosaprepitant - IVEMEND (CAP) - EMEA/H/C/000743/II/0031 67
15.3.15. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0024 68
15.3.16. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/II/0051/G 68
15.3.17. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0053 68
15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0006 68
15.3.19. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0122 69
15.3.20. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0027 69
15.3.21. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0032/G 69
15.3.22. Radium (^{223}Ra) - XOFIGO (CAP) - EMEA/H/C/002653/II/0014/G 69
15.3.23. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0011 70
15.3.24. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0042/G 70
15.3.25. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0009 70
15.3.26. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0061 71
15.3.27. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/X/0049/G 71

16. Annex I - Periodic safety update reports (PSURs) 71

16.1. PSUR procedures including centrally authorised products only 71

16.1.1. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201512 71
16.1.2. Canakinumab - ILARIS (CAP) - PSUSA/00000526/201512 71
16.1.3. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201512 72
16.1.4. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201512 72
16.1.5. Edoxaban - LIXIANA (CAP) - PSUSA/00010387/201512 72
16.1.6. Human fibrinogen, human thrombin - EVARREST (CAP); EVICEL (CAP); RAPLIXA (CAP); TACHOSIL (CAP) - PSUSA/00010297/201512 72

16.1.7. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201512 72
16.1.8. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201512 72
16.1.9. Lutetium (^{177}Lu) - LUMARK (CAP) - PSUSA/00010391/201512 72
16.1.10. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201512 73
16.1.11. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201512 73
16.1.12. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201512 73
16.1.13. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201512 73
16.1.14. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201512 73
16.1.15. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201512 73
16.1.16. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent - SYNFLORIX (CAP) - PSUSA/00009262/201512 73
16.1.17. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201512 74
16.1.18. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201512 (with RMP) 74
16.1.19. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201512 74
16.1.20. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201512 74
16.1.21. Thyrotropin alfa - THYROGEN (CAP) - PSUSA/00002940/201511 74
16.1.22. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201512 74
16.1.23. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201512 74
16.1.24. Verteporfin - VISUDYNE (CAP) - PSUSA/00003110/201512 75
16.1.25. Ziconotide - PRIALT (CAP) - PSUSA/00003142/201512 75
16.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) 75
16.2.1. Doxorubicin - CAELYX (CAP); MYOCET (CAP); NAP - PSUSA/00001172/201511 75
16.2.2. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201511 . 75
16.3. PSUR procedures including nationally approved products (NAPs) only 75
16.3.1. Alendronate, alfacalcidol (NAP) - PSUSA/00010308/201512 75
16.3.2. Atomoxetine (NAP) - PSUSA/00000262/201511 75
16.3.3. Clevidipine (NAP) - PSUSA/00010288/201511 75
16.3.4. Dexketoprofen (NAP) - PSUSA/00000997/201510 76
16.3.5. Diacerein (NAP) - PSUSA/00001026/201512 76
16.3.6. Indapamide (NAP) - PSUSA/00001731/201511 76
16.3.7. Minoxidil (non-topical formulations) - PSUSA/00002066/201510 76
16.3.8. Mycophenolic acid (apart from mycophenolate mofetil) (NAP) - PSUSA/00010243/201510 76
16.3.9. Naltrexone (NAP) - PSUSA/00002117/201511 76
16.3.10. Rimexolone (NAP) - PSUSA/00002647/201510 76
16.3.11. Salmeterol (NAP) - PSUSA/00002681/201510 77
16.3.12. Sultamicillin (NAP) - PSUSA/00002829/201511 77

16.3.13. Terazosin (NAP) - PSUSA/00002895/201511 77
16.3.14. Treprostinil (NAP) - PSUSA/00003013/201511 77
16.4. Follow-up to PSUR procedures 77
16.4.1. Aripiprazole - ABILIFY (CAP) - EMEA/H/C/000471/LEG 075 77
16.4.2. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/LEG 007 77
16.4.3. Colesevelam - CHOLESTAGEL (CAP) - EMEA/H/C/000512/LEG 031 78
16.4.4. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/LEG 010 78
17. Annex I – Post-authorisation safety studies (PASS) 78
17.1. Protocols of PASS imposed in the marketing authorisation(s) 78
17.1.1. Dinutuximab - UNITUXIN (CAP) - EMEA/H/C/PSP/0035.1 78
17.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/044.1 78
17.2. Protocols of PASS non-imposed in the marketing authorisation(s) 79
17.2.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019 79
17.2.2. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/MEA/012.5 79
17.2.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 006.2 79
17.2.4. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/MEA 012.3 79
17.2.5. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 167 79
17.2.6. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/MEA 001.1 80
17.2.7. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/MEA 011.3 80
17.2.8. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 023.3 80
17.2.9. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.1 80
17.2.10. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/MEA 026.2 80
17.3. Results of PASS imposed in the marketing authorisation(s) 81
17.4. Results of PASS non-imposed in the marketing authorisation(s) 81
17.4.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS0890/0107; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS0890/0077 81
17.4.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0050 81
17.4.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0040 81
17.4.4. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0055 81
17.4.5. Nepafenac - NEVANAC (CAP) - EMEA/H/C/000818/II/0033 81
17.4.6. Tacrolimus - PROTOPIC (CAP) - EMEA/H/C/000374/II/0063 82
17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation 82
17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002 82
17.5.2. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.7 82
17.5.3. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/MEA 002.3 82
17.5.4. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - OPTAFLU (CAP) - EMEA/H/C/000758/MEA 050.3 82

17.5.5. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/MEA 001.1 83
17.5.6. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.7 83
17.6. Others 83
17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.7 83
17.6.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.3 83
17.6.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.4 84
17.6.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.7 84
17.6.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.3 84
17.6.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.4 84
18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments 84
18.1. Annual reassessments of the marketing authorisation 85
18.1.1. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0064 (without RMP) 85
18.2. Conditional renewals of the marketing authorisation 85
18.2.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/R/0004 (without RMP)..... 85
18.2.2. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0035 (without RMP) 85
18.3. Renewals of the marketing authorisation 85
18.3.1. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/R/0036 (without RMP) 85
18.3.2. Azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/R/0018 (without RMP) 85
18.3.3. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/R/0024 (without RMP) 85
18.3.4. Desloratadine - DESLORATADINE ACTAVIS (CAP) - EMEA/H/C/002435/R/0008 (without RMP) 86
18.3.5. Efavirenz - EFAVIRENZ TEVA (CAP) - EMEA/H/C/002352/R/0018 (without RMP) 86
18.3.6. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/R/0065 (without RMP) 86
18.3.7. Levetiracetam - LEVETIRACETAM ACTAVIS (CAP) - EMEA/H/C/002355/R/0013 (without RMP) 86
18.3.8. Levetiracetam - LEVETIRACETAM SUN (CAP) - EMEA/H/C/002051/R/0013 (without RMP) . 86
18.3.9. Pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/R/0049 (without RMP) 86
18.3.10. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/R/0023 (without RMP) 87
18.3.11. Repaglinide - REPAGLINIDE ACCORD (CAP) - EMEA/H/C/002318/R/0005 (without RMP)... 87
18.3.12. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/R/0062 (with RMP) 87
18.3.13. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/R/0034 (without RMP)..... 87
19. Annex II – List of participants 87
20. Annex III - List of acronyms and abbreviations 92
21. Explanatory notes 93

1. Introduction

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

The Chairperson opened the 4-8 July 2016 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II – List of participants). No new or additional conflicts were declared.

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 taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson announced that Ingebjørg Buajordet was to step down as PRAC member for Norway after the current PRAC plenary meeting. The PRAC thanked her for her important contribution to the work of the PRAC since the committee's establishment.

Finally, the PRAC welcomed the new Slovakian presidency of the Council of the EU.

1.2. Agenda of the meeting of 04-08 July 2016

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

1.3. Minutes of the previous meeting on 06-09 June 2016

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

Post-meeting note: the PRAC minutes of the meeting held on 6-9 June 2016 were published on the EMA website on 26 August 2016 (EMA/PRAC/460046/2016).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

2.4. Planned public hearings

None

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

3.1. Newly triggered procedures

3.1.1. Paracetamol (NAP) (modified release formulation) - EMEA/H/A-31/1445

Applicant: GlaxoSmithKline Consumer Healthcare AB (Alvedon, 665 mg Modified-Release tablet), various

PRAC Rapporteur: Veerle Verlinden; PRAC Co-rapporteur: Qun-Ying Yue

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

Background

Paracetamol, an analgesic and antipyretic, is indicated for the treatment of headache, toothache, cold-related fever, menstrual cramps, muscle and joint pain, as well as for rheumatic pain, hyperpyrexia, and also for chronic pain and other conditions that require continuous dosing. Some paracetamol-containing products, intended to have a longer action are available in the EU, as Alvedon 665 mg and associated names, and other modified- and prolonged-release paracetamol products.

The Swedish Medicines Agency (MPA) sent a letter of notification dated 30/06/2016 of a referral under Article 31 of Directive 2001/83/EC for the review of modified- and prolonged-release paracetamol-containing medicines following the recent publication by *Salmonson H et al.*[1] of a retrospective pharmacokinetic (PK) and clinical analysis concluding that the standard N-acetylcysteine treatment protocol, designed for management of overdose with immediate-release paracetamol-containing products is inadequate following overdose after administration of extended release paracetamol-containing products. It was considered of Union interest to assess ways to minimise the harm in case of overdosing with modified- and prolonged-release formulations and to consider whether the recommendations to manage such cases can be further improved. In addition, measures to minimise the risk for poisoning with modified- and prolonged-release formulations should be considered, taking into account the benefit-risk balance for all indications of such formulations where the benefit of prolonged exposure and pain relief is weighed against an increased risk of serious harm following overdose.

Discussion

The PRAC noted the notification letter from the MPA and discussed a list of questions (LoQ)

[1] Salmonson H, et al.: The standard treatment protocol is inadequate following overdose of extended release paracetamol: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol 2016;54:424 (Abstract 124)

to be addressed by the MAHs of modified- and prolonged-release paracetamol containing products, as well as a timetable for conducting the review. In addition, the PRAC agreed a LoQ to Poisons Centres to further investigate any possible evidence of an increased risk of overdose harm with modified- and prolonged-release tablets containing paracetamol.

The PRAC appointed Veerle Verlinden as Rapporteur and Qun-Ying Yue as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a LoQ to the MAHs of paracetamol modified- and prolonged-release tablets (EMA/PRAC/451078/2016) and a timetable for the procedure (EMA/PRAC/460935/2016). In addition, the PRAC agreed a LoQ to Poisons Centres in Member States where the concerned products are authorised.

3.1.2. Retinoids: acitretin (NAP); adapalene (NAP); alitretinoin - PANRETIN (CAP); bexarotene – TARGRETIN (CAP); isotretinoin (NAP); tazarotene (NAP); tretinoin (NAP) - EMEA/H/A-31/1446

Applicant: Eisai Ltd (Panretin, Targretin), various

PRAC Rapporteur: Leonor Chambel; PRAC Co-rapporteur: Julie Williams

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

Background

The United Kingdom's Medicines Agency (MHRA) sent a letter of notification dated 07/07/2016 of a referral under Article 31 of Directive 2001/83/EC for retinoid-containing medicines (acitretin; adapalene; alitretinoin; bexarotene; isotretinoin; tazarotene; tretinoin) indicated for the treatment of several conditions mainly affecting the skin such as acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders[2], to evaluate measures currently in place for pregnancy prevention and for minimising the possible risk of neuropsychiatric disorders for oral and topical retinoids. This notification followed previous PRAC discussion when PRAC reviewed the effectiveness of the pregnancy prevention programmes (PPP) in the context of a recent PSUSA procedure for oral isotretinoin (PSUSA/00001795/201505). The PRAC noted that post-marketing data and published studies raised concerns on the way requirements of the PPP are followed in practice. Further discussion in the context of PSUSA procedures for erythromycin plus isotretinoin topical gels (PSUSA/00001796/201508) and for acitretin (PSUSA/00000051/201510) also showed concerns about the consistency and effectiveness of existing risk minimisation for medicinal products containing these substances in combination. Following a non-urgent information (NUI) request across the EU and its compilation, this confirmed the need to review product information and other risk minimisation measures across the class of retinoids. For further background, see PRAC minutes January 2016, PRAC minutes April 2016 and PRAC minutes June 2016.

In addition, during these PSUSA discussions the PRAC noted that the possible risk of neuropsychiatric disorders associated with retinoids remains of concern. Therefore, the PRAC considered it is important to review the possible risk of neuropsychiatric disorders

[2] Tretinoin may also be used to treat promyelocytic leukaemia

with retinoids together with the extent and nature of the various warnings described in product information across the EU to ensure that they reflect the available evidence for oral and topical retinoids.

Discussion

The PRAC noted the notification letter from MHRA and discussed a list of questions (LoQ) to be addressed by the MAHs of retinoid-containing products as well as a timetable for conducting the review.

The PRAC appointed Leonor Chambel as Rapporteur and Julie Williams as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a LoQ to the MAHs of retinoids containing products (EMA/PRAC/461926/2016) and a timetable for the procedure (EMA/PRAC/461927/2016).

3.1.3. Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE (CAP), KOVALTRY (CAP) - EMEA/H/A-31/1448

Applicant: Baxter AG (Advate), Bayer Pharma AG (Helixate Nexgen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Pfizer Limited (Refacto AF), various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Brigitte Keller-Stanislawski

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

Background

The German Medicines Agency for vaccines and biomedicines (Paul-Ehrlich-Institut (PEI)) sent a letter of notification dated 06/07/2016 of a referral under Article 31 of Directive 2001/83/EC for the review of factor VIII-containing medicines indicated for the treatment of haemophilia A following a recent publication of the SIPPET study *by Peyvandi et al.*[3] in the New England Journal of Medicine, in which the authors suggested that inhibitors develop more frequently in patients receiving factor VIII medicines produced by DNA[4] recombinant technology than those receiving factor VIII medicines derived from blood. The PRAC agreed that the new data should be thoroughly evaluated in the context of all other data relevant to the development of inhibitor antibodies directed towards blood derived and recombinant factor VIII medicines. The review should also consider any potential for risk minimisation measures or other changes to the marketing authorisations of these medicinal products. For further background, see also under 4.2.2.

Discussion

The PRAC noted the notification letter from PEI and discussed a list of questions (LoQ) to be

[3] F. Peyvandi et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N. Eng.l J. Med. 2016 May 26;374(21):2054-64) (SIPPET study)
[4] Deoxyribonucleic acid

addressed during the procedure as well as a timetable for conducting the review.

The PRAC appointed Rafe Suvarna as Rapporteur and Brigitte Keller-Stanislawski as Co-Rapporteur for the procedure.

Summary of recommendation(s)/conclusions

The Committee adopted a LoQ (EMA/PRAC/471535/2016) and a timetable for the procedure (EMA/PRAC/471536/2016).

3.2. Ongoing procedures

3.2.1. Direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free): daclatasvir – DAKLINZA (CAP); dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP); simeprevir - OLYSIO (CAP); sofosbuvir – SOVALDI (CAP); sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/A-20/1438

Applicant: Bristol-Myers Squibb Pharma EEIG (Daklinza); AbbVie Ltd (Exviera, Viekirax); Janssen-Cilag International N.V. (Olysio); Gilead Sciences International Ltd (Harvoni, Sovaldi)

PRAC Rapporteur: Margarida Guimarães; PRAC Co-rapporteur: Dolores Montero Corominas

Scope: Review of the benefit-risk balance of DAAV following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free) (daclatasvir (Daklinza), dasabuvir (Exviera), ombitasvir/paritaprevir/ritonavir (Viekirax), simeprevir (Olysio), sofosbuvir (Sovaldi), sofosbuvir/ledipasvir (Harvoni)) to assess the risk of hepatitis B reactivation and the risk of unexpected early hepatocellular carcinoma (HCC) recurrence in patients treated with a DAAV and to establish whether any measures are necessary to minimise these risks. For further background, see PRAC minutes March 2016 and PRAC minutes April 2016.

Summary of recommendation(s)/conclusions

The PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs in accordance with a revised timetable for conducting the review (EMA/PRAC/196120/2016 Rev.2). In addition, the PRAC adopted a list of questions (LoQ) and endorsed a list of experts for the Scientific Advisory Group on human immunodeficiency virus (HIV)/viral diseases (SAG HIV/Viral Diseases) scheduled on 10 October 2016.

3.2.2. Gadolinium-containing contrast agents (GdCA): gadobenic acid (NAP); gadobutrol (NAP); gadodiamide (NAP); gadopentetic acid (NAP); gadoteric acid (NAP); gadoteridol (NAP); gadoxetic acid (NAP); gadoversetamide – OPTIMARK (CAP) - EMEA/H/A-31/1437

Applicant: Mallinckrodt Deutschland GmbH (Optimark); various

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Doris Stenver

Scope: Review of the benefit-risk balance following notification by the European

Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for gadolinium-containing contrast agents (GdCAs) to review the issue of accumulation of gadolinium in the brain, its clinical consequences and the overall safety profile of GdCAs. For further background, see PRAC minutes March 2016 and PRAC minutes June 2016.

Summary of recommendation(s)/conclusions

The PRAC adopted a list of experts for an ad-hoc expert group meeting scheduled on 5 September 2016.

3.2.3. Sodium-glucose co-transporter 2 (SGLT2) inhibitors[5]: Canaglifozin – INVOKANA (CAP); canagliflozin, metformin – VOKANAMET (CAP); dapaglifozin – EDISTRIDE (CAP), FORXIGA (CAP); dapaglifozin, metformin – XIGDUO (CAP), EBYMECT (CAP); empaglifozin – JARDIANCE (CAP); empaglifozin, metformin – SYNJARDI (CAP) - EMEA/H/A-20/1442

Applicant: Janssen-Cilag International N.V. (Invokana; Vokanamet); AstraZeneca AB (Edistride, Forxiga; Xigduo, Ebymect); Boehringer Ingelheim International GmbH (Jardiance; Synjardi)

PRAC Rapporteur: Valerie Strassmann; PRAC Co-rapporteur: Menno van der Elst

Scope: Extension of the scope of the review of the benefit-risk balance to all sodium-glucose co-transporter-2 (SGLT2) inhibitors following notification by European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for canagliflozin-containing medicines to review the potential increased risk of lower limb amputation following observation of such an increased risk (primarily of the toe) in ongoing clinical trials[6], to assess ways to minimise this risk and to evaluate its impact on the benefit-risk balance of canagliflozin-containing medicines. In the notification letter dated 15/04/2016 initiating the procedure, the European Commission (EC) also requested the EMA to consider whether this review should be extended to other sodium-glucose co-transporter-2 (SGLT2) inhibitors if necessary, given that they all share the same mechanism of action. In April 2016, the PRAC had agreed a list of questions to the MAHs of other SGLT2 inhibitors (dapagliflozin- and empagliflozin-containing medicines) to further investigate any possible evidence of an increased risk of lower limb amputation. For further background, see PRAC minutes April 2016 and PRAC minutes June 2016.

Discussion

The PRAC considered the EC's request to consider extending the scope of the ongoing Article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicines to other

[5] previously canagliflozin only
[6] CANVAS: randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus; CANVAS-R: Randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with type 2 diabetes mellitus

SGLT2 inhibitors. Based on the available data, the PRAC agreed by majority to advise EC that a class effect could not be excluded in light of the current evidence. See dapagliflozin under 10.3.1. and empagliflozin under 10.3.2. Therefore, the EC broadened the scope of the ongoing procedure to the whole class of SGLT2-inhibitors to allow a review of data on the risk of amputation, including reports from post-marketing and any other sources of data, and their impact on the benefit-risk balance of all products in the SGLT2 class. As a consequence, the EC sent an addendum to the notification dated 06/07/2016 to include dapagliflozin and empagliflozin-containing medicines to the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 for the review of all SGLT2 inhibitor-containing medicines and requested the EMA to give its opinion by 31 March 2017.

The PRAC noted the addendum to the notification letter from the EC and discussed an addendum to the previous list of questions (LoQ) to be addressed by the MAHs for the other SGLT2 inhibitors as well as a revised timetable for conducting the review.

The PRAC had previously appointed Valerie Strassmann as Rapporteur and Menno van der Elst as Co-Rapporteur for this procedure.

Summary of recommendation(s)/conclusions

The Committee adopted an addendum to the LoQ (EMA/PRAC/196081/2016) and a revised timetable for the procedure (EMA/PRAC/196120/2016 Rev.1).

3.3. Procedures for finalisation

3.3.1. Idelalisib – ZYDELIG (CAP) - EMEA/H/A-20/1439

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance of idelalisib following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004 based on pharmacovigilance data

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Zydelig (idelalisib) reviewing findings from the interim results of three clinical trials[7] together with all available safety data related to idelalisib is to be concluded. The review was initiated following an increased rate of death and serious adverse events (SAE) amongst subjects receiving idelalisib compared to control groups, observed in these clinical trials, to assess the potential impact of the new data on the benefit-risk balance of Zydelig in the approved indications and the ongoing extension of indication for use in combination with ofatumumab in chronic lymphocytic leukaemia (CLL) (variation II/011). For further background, see PRAC minutes March 2016, PRAC minutes May 2016 and PRAC minutes June 2016.

Discussion

[7] GS-US-312-0123: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated chronic lymphocytic leukaemia
GS-US-313-0124: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with rituximab for previously treated indolent non-Hodgkin lymphomas
GS-US-313-0125: Phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of idelalisib (GS 1101) in combination with bendamustine and rituximab for previously treated indolent non-Hodgkin lymphomas

The PRAC reviewed the totality of the data submitted by the MAH and the views expressed by the Scientific Advisory Group in oncology (SAG-O).

The PRAC noted that studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 involved patient groups and treatment combinations different from those of the authorised indications of Zydelig. The PRAC considered the results of these studies of limited relevance for the benefit-risk balance of idelalisib in its authorised indications and ongoing extension of indication in combination with ofatumumab for the treatment of CLL. Nevertheless, as a precaution and in view of the fact that limited data are available in treatment-naïve CLL patients with 17p deletion or TP53 mutation, the PRAC recommended that idelalisib should only be used in this group of patients if they are not eligible for any other therapies.

The PRAC noted that most of the serious adverse events reported in studies GS-US-312-0123, GS-US-313-0124 and GS-US-313-0125 were related to infections. The PRAC considered that strengthened minimisation measures for the known risk of infection related to the use of idelalisib were necessary, with some refinements to the 'provisional measures' recommended in March 2016. To this effect, the PRAC recommended that treatment with idelalisib should not be initiated in patients with evidence of systemic infections, that patients should be monitored for respiratory symptoms and that they should be administered *Pneumocystis jirovecii* pneumonia prophylaxis throughout and after idelalisib treatment. Regular clinical and laboratory monitoring for cytomegalovirus (CMV) infection is also recommended in patients with evidence of prior infection. In addition, neutrophil count monitoring is recommended. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution.

Overall, the PRAC concluded that the benefit-risk balance of Zydelig (idelalisib) remains favourable subject to the agreed amendments to the product information.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus, a recommendation to vary the terms of the marketing authorisation(s) for Zydelig (idelalisib), to be considered by the CHMP for an opinion. See EMA Press Release (EMA/459461/2016) entitled 'PRAC concludes review of Zydelig and issues updated recommendations for use'. The PRAC also agreed the distribution of a Direct Healthcare Professional Communication (DHPC) together with a communication plan.

Post-meeting note: the press release entitled 'CHMP confirms recommendations for use of Zydelig Patients should be monitored for infection and given antibiotics during and after treatment' (EMA/488322/2016) representing the opinion adopted by the CHMP was published on the EMA website on 22 July 2016.

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request

None

3.5. Others

None

4. Signals assessment and prioritisation[8]

4.1. New signals detected from EU spontaneous reporting systems

See also Annex I 14.1. **Error! Reference source not found.**

4.1.1. Acenocoumarol (NAP), fluindione (NAP), phenindione (NAP), phenprocoumon (NAP)

Applicant: various

PRAC Rapporteur: Martin Huber

Scope: Signal of calciphylaxis

EPITT 18710 – New signal

Lead Member States: DE, BG

Background

Acenocoumarol, fluindione, phenindione and phenprocoumon are vitamin K antagonists indicated, as antithrombotic agents, for the treatment and prevention of thromboembolic diseases.

In May 2016, the PRAC adopted a recommendation on a signal of calciphylaxis associated with warfarin, requesting MAHs of warfarin-containing medicinal products to update their product information to include calciphylaxis as a new warning and a new undesirable effect. For further background, see PRAC minutes May 2016. Based on the available evidence and the possible mechanism related to the mode of action shared by the whole class of vitamin K antagonists (VKA) (acenocoumarol, fluindione, phenindione and phenprocoumon), Bulgaria and Germany performed reviews in EudraVigilance and the published literature for evidence of such an association between other vitamin K antagonists and calciphylaxis. Further to the reviews, a signal of calciphylaxis also called calcific uremic arteriolopathy (CUA) was identified by Bulgaria. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and in the literature and requested a cumulative review of all cases of calciphylaxis and other related MedDRA PT[9] with a view to amending the product information and the RMP as applicable for acenocoumarol, fluindione, phenindione and phenprocoumon-containing medicines.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for acenocoumarol-, fluindione-, phenindione- and phenprocoumon-containing products (Meda Pharma, Merck Santé S.A.S, Novartis, Merus Labs Luxco, Mercury Pharma Group) should submit to EMA, within 90 days, a

[8] 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.
[9] Medical dictionary for regulatory activities - preferred terms

cumulative review of all cases of calciphylaxis and MedDRA PT related terms, including a review of published literature, as well as preclinical and in vitro data, and a discussion on the possible mechanism of action. In addition, the MAHs should submit a proposal for amending the product information and the RMP as applicable.

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

4.1.2. Ceftriaxone (NAP)

Applicant: various

PRAC Rapporteur: Not applicable

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

EPITT 18715 – New signal

Lead Member State: LV

Background

Ceftriaxone is a beta-lactam antibacterial, a third-generation cephalosporin, indicated for the treatment of various infections in adults and children, including bacterial meningitis, community or hospital acquired pneumonia, acute otitis media, intra-abdominal infections, complicated urinary tract infections, bone and joint infections, and complicated skin and soft tissue infections.

During routine signal detection activities, a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) was identified by Latvia, based on 7 cases retrieved from EudraVigilance. Latvia confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the 7 case reports of DRESS that were fully documented. The PRAC agreed that the number of possible cases of DRESS with a temporal relationship to ceftriaxone was very low and in the light of the current knowledge, there was insufficient evidence to support a causal relationship.

Summary of recommendation(s)

- The MAHs for ceftriaxone-containing products should continue to monitor any cases of drug reaction with eosinophilia and systemic symptoms (DRESS) events as part of routine safety surveillance.

4.1.3. Loperamide (NAP)

Applicant: various

PRAC Rapporteur: Nectaroula Cooper

Scope: Signal of serious cardiac events with high doses of loperamide, mainly from abuse and misuse

EPITT 18339 – New signal

Lead Member State(s): CY, EE, PL

Background

Loperamide is an antidiarrheal, intestinal anti-inflammatory and anti-infective agent, indicated for the treatment of symptoms of diarrhoea.

Following the publication on 7 June 2016 by the FDA of a drug safety communication warning relating to serious heart problems associated with loperamide, mainly at high doses through abuse and misuse, a signal of QT prolongation and torsade de pointes was identified by Cyprus based on 54 cases reported since January 2016, including 12 where causality could not be ruled out. Cyprus confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the literature and case reports in EudraVigilance. Taking into account the 54 cases reported since January 2016 including 12 where causality could not be ruled out, the PRAC agreed to request the MAH of the loperamide originator product (i.e. Imodium, Johnson & Johnson Consumer B.V) to provide a cumulative review of all cases of torsade de pointes/QT prolongation MedDRA SMQ[10] (broad) in the context of high doses of loperamide, including cases from abuse and misuse, as well as all relevant data from spontaneous reports, clinical trials and relevant literature. In addition, the MAH should provide an evaluation of the biological plausibility for a possible association, and a comparative assessment of the incidence of the cases reported in the EU and the US. Based on its review, the MAH should discuss the need for an update of the product information and/or the RMP and should include a proposal for amendments as appropriate. Moreover, the MAH should propose any additional measures that may be deemed necessary as a result of the review.

The PRAC appointed Nectaroula Cooper as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for loperamide originator product should submit to EMA, within 90 days, a cumulative review of all cases of torsade de pointes/QT prolongation in the context of high doses of loperamide, including cases from abuse and misuse, as well as all relevant data from spontaneous reports, clinical trials and relevant literature. In addition, the MAH should provide an evaluation of the biological plausibility for a possible association, and a comparative assessment of the incidence of the cases reported in the EU and the US. Based on its review, the MAH should discuss the need for an update of the product information and/or the RMP and should include a proposal for amendments as appropriate. Moreover, the MAH should propose any additional measures that may be deemed necessary as a result of the review.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.4. Vildagliptin – GALVUS (CAP), JALRA (CAP), XILIARX (CAP); vildagliptin, metformin – EUCREAS (CAP), ICANDRA (CAP), ZOMARIST (CAP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

[10] Medical dictionary for regulatory activities – standard MedDRA query

Scope: Signal of pemphigoid

EPITT 18692 – New signal

Lead Member State: SE

Background

Vildagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor indicated for the treatment of type 2 diabetes mellitus in monotherapy or in combination, including with metformin.

The exposure to vildagliptin is estimated to have been about 4.4 million patient-years worldwide and 6.8 million patient-years for vildagliptin in combination with metformin, in the period from first authorisation in 2007 to 28 February 2015.

During routine signal detection activities, a signal of pemphigoid was identified by EMA, following a PMDA[11] early notification of a labelling change dated 01/04/2016, based also on recent publications including data from French regional pharmacovigilance centres and on 16 cases retrieved in EudraVigilance suggesting evidence for a causal association. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance and in the literature, including the disproportionality score for vildagliptin. The PRAC agreed to request the MAH to conduct a cumulative review of all cases of phemphigoid associated with vildagliptin-containing products, including all relevant data from spontaneous reports, clinical trials and relevant literature, together with an assessment of the biological plausibility for a possible association, with a view to amending the product information for vildagliptin-containing medicines.

Summary of recommendation(s)

- The MAH for vildagliptin-containing products (Novartis Europharm Limited) should submit to EMA, within 90 days, a cumulative review of cases of pemphigoid from spontaneous reports, clinical trials and relevant literature. This should include details on time to onset, time to recovery in relation to both de-challenge and to start of active pemphigoid therapy as well as possible rechallenge. In addition, the MAH should provide a detailed discussion on background incidence of pemphigoid in the target population, the expected course of the disease after standard of care, disease aetiology as well as plausible mechanisms through which DPP-4 inhibitors could cause pemphigoid. The MAH should also discuss the need for any potential amendment to the product information and/or the RMP as appropriate.
- 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 also Annex I 14.2. **Error! Reference source not found.**

4.2.1. Fluoroquinolones (systemic use): Ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin (NAP);

[11] Japanese Pharmaceuticals and Medical Devices Agency

lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

Applicant: Bayer, Sanofi, various

PRAC Rapporteur: Martin Huber

Scope: Signal of uveitis

EPITT 18686 – New signal

Lead Member State: DE

Background

Fluoroquinolones are broad-spectrum antibiotics indicated for a variety of infections including serious bacterial infections, especially hospital-acquired infections, and others caused by susceptible microorganisms. Some fluoroquinolones have restricted indications limited to situations where other commonly recommended antibacterials are not appropriate.

During the evaluation of a recent PSUSA procedure for ofloxacin (systemic use) (PSUSA/00002203/201504, see PRAC minutes December 2015), a signal of uveitis was identified by Denmark, based on a literature review. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the evidence from the literature and considered that a further analysis of available data in EudraVigilance was warranted before any conclusion can be drawn. In addition, a literature review[12] should be conducted on a possible association between systemic fluoroquinolones and uveitis, in the light of patient exposure, with a view to discussing a signal follow-up at the November 2016 PRAC meeting[13].

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- EMA should perform a further analysis of data available in EudraVigilance while the Rapporteur will conduct a literature review regarding a possible association between systemic fluoroquinolones and uveitis, in the light of patient exposure.
- Further discussion will be held at the November 2016 PRAC meeting.

4.2.2. Human coagulation(plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A) (NAP); human coagulation factor VIII (inhibitor bypassing fraction) (NAP); human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP)
Recombinant factor VIII: antihemophilic factor (recombinant) (NAP); moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), IBLIAS (CAP), KOGENATE

[12] Hinkle DM, Dacey MS, Mandelcorn E, Kalyani P, Mauro J, Bates JH, et al. Bilateral uveitis associated with fluoroquinolone therapy. Cutan Ocul Toxicol. 2012 Jun, 31:111–6
Forooghian F, Maberley D, Albiani DA, Kirker AW, Merkur AB, Etminan M. Uveitis risk following oral fluoroquinolone therapy: a nested case-control Study. Ocul Immunol Inflamm. 2013 Oct;21(5):390–3
Eadie B, Etminan M, Mikelberg FS. Risk for uveitis with oral moxifloxacin: a comparative safety study. JAMA Ophthalmol. 2015 Jan, 133(1):81–4
Sandhu HS, Brucker AJ, Ma L, VanderBeek BL. Oral fluoroquinolones and the risk of uveitis. JAMA Ophthalmol. 2015 Oct 29:1-6
[13] Scheduled on 24-27 October 2016

(CAP), KOVALTRY; simoctocog alfa – NUWIQ (CAP); turoctocog alfa – NOVOEIGHT (CAP)

Applicant: Baxter AG (Advate), Bayer Pharma AG (Helixate NexGen, Iblias, Kogenate, Kovaltry), CSL Behring GmbH (Voncento), Novo Nordisk A/S (NovoEight), Octapharma AB (Nuwiq), Pfizer Limited (ReFacto AF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived *vs* recombinant coagulation factor VIII concentrates

EPITT 18701 – New signal

Lead Member State: DE

Background

Factor VIII-containing medicines are anti-haemorrhagic agents indicated for the treatment of congenital haemophilia A.

Following a recent publication in the New England Journal of Medicine (NEJM) of the SIPPET study by *Peyvandi et al.*[14], a signal of development of inhibitors against factor VIII in previously untreated patients was identified by Germany, suggesting that patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from the recently published SIPPET study, and agreed that the development of inhibitors in patients treated with plasma-derived or recombinant coagulation factor VIII products required a thorough evaluation.

The PRAC appointed Brigitte Keller-Stanislawski as Rapporteur for the signal.

Summary of recommendation(s)

Germany sent a letter of notification dated 06/07/2016 of a referral procedure under Article 31 of Directive 2001/83/EC to assess the potential impact of the results on the marketing authorisations of factor VIII-containing products including risk minimisation measures. See factor VIII under 3.1.3.

4.2.3. Methylphenidate (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of priapism

EPITT 18719 – New signal

Lead Member State: UK

[14] F. Peyvandi et al. A randomized trial of Factor VIII and neutralizing antibodies in haemophilia A. N. Eng.l J. Med. 2016 May 26;374(21):2054-64 (SIPPET study)

Background

Methylphenidate, a psychostimulant centrally active sympathomimetic, is indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

A signal of priapism was identified by the United Kingdom, based on 8 cases reported with the originator medicinal product including one positive dechallenge, a literature review including the paper from *Eiland et al.*[15], a Med Alert from the FDA dated 2013 and the recent PSUSA procedure concluded in June 2016 (PSUSA/00002024/201510; see PRAC minutes June 2016). The United Kingdom confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the available evidence from case reports in EudraVigilance, the literature and information from other regulatory authorities on cases of priapism. The PRAC agreed that the MAHs of methylphenidate-containing products involved in the recent PSUSA procedure should provide updated cumulative reviews of priapism and associated terms using the MedDRA HLT[16] 'erection and ejaculation conditions and disorders' and consider amending the product information and/or the RMP as applicable. In their reviews, MAHs should consider the potential serious sequelae and provide details on the patient's age, time to onset of the reaction, underlying conditions, concomitant medications, context of event occurrence including whether it occurred on withdrawal of treatment, dosage, de- and re-challenge information and formulation (i.e. instant release or 'longer-acting').

The PRAC appointed Julie Williams as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for methylphenidate-containing products involved in the recently concluded PSUSA procedure (Novartis pharma GmbH, Janssen-Cilag, Shire Pharmaceuticals, Sandoz, Johnson & Johnson, Alternova A/S, Proton Pharma S.A., Medice Arzneimittel Putter GmbH & Co.KG, Generics (UK) Limited trading as Mylan and Laboratorios Rubió) should submit to EMA, within 90 days, updated cumulative reviews of the signal, including an analysis of all case reports of priapism and related terms, and a proposal for amending the product information and/or the RMP as applicable. In their reviews, MAHs should consider the potential serious sequelae.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Ferrous sulfate (NAP)

Applicant: various

PRAC Rapporteur: Leonor Chambel

Scope: Signal of mouth ulceration

EPITT 18623 – Follow-up to March 2016

[15] Eiland LS et al (2014) Priapism associated with the use of stimulant medications and atomoxetine for attention-deficit/hyperactivity disorder in children. Ann Pharmacother 48; 1350-5.
[16] Medical dictionary for regulatory activities - high level term level

Background

For background information, see PRAC minutes March 2016.

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

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the data submitted by the MAHs, and the known association of ferrous sulfate with local mucosal irritation, the PRAC agreed that the MAHs of oral solid formulations of ferrous sulfate-containing medicinal products should submit a variation, to amend the product information with respect to this signal of mouth ulceration.

Summary of recommendation(s)

- The MAHs of oral solid formulations of ferrous sulfate-containing medicines should submit to EMA or to the national competent authorities of the MSs as applicable, within 90 days, a variation for amending the product information[17].

For the full PRAC recommendation, see EMA/PRAC/452657/2016 published on 02/08/2016 on the EMA website.

4.3.2. Human albumin solutions (NAP)

Applicant: various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of increased risk of mortality in patients with severe traumatic brain injury and in patients with burns

EPITT 13948 – Follow-up to November 2012

Background

For background information, see PRAC minutes November 2012.

The Member States replied to the non-urgent information (NUI) request on the signal of increased risk of mortality in patients with severe traumatic brain injury and in patients with burns, and the responses were assessed by the Rapporteur.

Discussion

Considering that there is insufficient evidence to support a causal relationship between the use of human albumin and an increased risk of mortality in patients with severe traumatic brain injury and in patients with burns, and that there is no biological explanation for a risk of higher mortality in patients with severe traumatic brain injury, the PRAC agreed that the signal could be closed.

Summary of recommendation(s)

- The PRAC agreed that the signal of increased risk of mortality associated with human albumin in patients with severe traumatic brain injury and in patients with burns may be closed.

[17] Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is to be updated accordingly

- The PRAC agreed to transmit to the CHMP Blood Product Working Party (BPWP) its recommendation for consideration at the time of updating the Guideline on the core SmPC of human albumin solution (EMA/CHMP/BPWP/494462/2011 rev.3) as considered appropriate.

4.3.3. Proton pump inhibitors (PPIs): Dexlanzoprazole (NAP), esomeprazole – NEXIUM CONTROL (CAP), NAP; lansoprazole (NAP); omeprazole (NAP); pantoprazole – CONTROLOC CONTROL (CAP) - EMEA/H/C/001097/SDA/015, PANTECTA CONTROL (CAP) - EMEA/H/C/001099/SDA/015, PANTOLOC CONTROL (CAP) - EMEA/H/C/001100/SDA/014, PANTOZOL CONTROL (CAP) - EMEA/H/C/001013/SDA/015, SOMAC CONTROL (CAP) - EMEA/H/C/001098/SDA/020, NAP; rabeprazole (NAP)

Applicant: Pfizer Consumer Healthcare Ltd (Nexium Control), Takeda GmbH (Controloc Control, Pantecta Control, Pantoloc Control, Pantozol Control, Somac Control), various

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of elevated circulating levels of chromogranin A

EPITT 18614 – Follow-up to March 2016

Background

For background information, see PRAC minutes March 2016.

The MAHs replied to the request for information on the signal of elevated circulating levels of chromogranin A and the responses were assessed by the Rapporteur.

Discussion

The PRAC agreed that it would be useful to update the product information with respect to this signal of elevated circulating levels of chromogranin A and its implications in the monitoring of patients with neuroendocrine tumours.

Summary of recommendation(s)

- The MAHs of rabeprazole-, lansoprazole-, dexlansoprazole-, pantoprazole-, esomeprazole- and omeprazole-containing products should submit a variation to EMA or to the national competent authorities of the MSs as applicable, within 90 days, to amend the product information[18].

For the full PRAC recommendations, see EMA/PRAC/452657/2016 published on 02/08/2016 on the EMA website.

4.3.4. Tramadol, paracetamol (NAP)

Applicant: various

PRAC Rapporteur: Julie Williams

Scope: Signal of hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

EPITT 18471 – Follow-up to March 2016

[18] Update of SmPC sections 4.4 and 5.1. The package leaflet is to be updated accordingly

Background

For background information, see PRAC minutes March 2016.

The MAH replied to the request for information on the signal of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion and the responses were assessed by the Rapporteur.

Discussion

Based on the available evidence from the literature and spontaneous reports, the PRAC agreed that the data do not suggest a causal association between treatment with tramadol and the occurrence of hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) as the number of cases is very low in view of the extensive post-authorisation exposure and also many of the reported cases occurred in elderly patients and were confounded by concomitant therapy or other factors. In light of the limitations of the evidence, the PRAC concluded that changes to the product information were not warranted at this stage.

Summary of recommendation(s)

- The MAHs for tramadol-containing products should continue to monitor hyponatremia and syndrome of inappropriate antidiuretic hormone secretion as part of routine safety surveillance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided advice to the 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. **Error! Reference source not found.**

5.1.1. Bezlotoxumab - EMEA/H/C/004136

Scope: Prevention of *Clostridium difficile* infection (CDI) recurrence

5.1.2. Dasabuvir, ombitasvir, paritaprevir, ritonavir - EMEA/H/C/004235

Scope: Treatment of hepatitis C

5.1.3. Edotreotide - EMEA/H/C/004140, Orphan

Applicant: Advanced Accelerator Applications

Scope: Diagnosis of gastro-entero-pancreatic neuroendocrine tumours

5.1.4. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue - EMEA/H/C/004258, Orphan

Applicant: Tigenix, S.A.U.; ATMP[19]

Scope: Treatment of complex perianal fistula(s)

5.1.5. Follitropin delta - EMEA/H/C/003994

Scope: Controlled ovarian stimulation

5.1.6. Human immunoglobulin (Ig)G1 monoclonal antibody specific for human interleukin-1 alpha - EMEA/H/C/004388

Scope (accelerated assessment): Treatment of metastatic colorectal cancer

5.1.7. Obeticholic acid - EMEA/H/C/004093, Orphan

Applicant: Intercept Italia s.r.l

Scope: Treatment of primary biliary cirrhosis

5.1.8. Pegfilgrastim - EMEA/H/C/004342; EMEA/H/C/004023

Scope: Treatment of neutropenia

5.1.9. Venetoclax - EMEA/H/C/004106, Orphan

Applicant: AbbVie Ltd.

Scope: Treatment of adult patients with chronic lymphocytic leukaemia (CLL)

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

See also Annex I 15.2. 14.1. **Error! Reference source not found.**

5.2.1. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/II/0103

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Eva Segovia

Scope: Submission of an updated RMP (version 9.0) in order to add hepatitis B reactivation as a new important identified risk

Background

Imatinib, a protein-tyrosine kinase inhibitor, is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment, with Ph+ CML in the chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis, with newly diagnosed

[19] Advanced-therapy medicinal product

Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy, with relapsed or refractory Ph+ ALL as monotherapy, with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. Imatinib is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), as adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST, and for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

The PRAC is evaluating a type II variation procedure for Glivec, a centrally authorised product containing imatinib, to update the RMP to reflect the introduction of Hepatitis B reactivation as a new important identified risk. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see PRAC minutes September 2015 and PRAC minutes February 2016.

Summary of advice

- The RMP version 9.0 for Glivec (imatinib) in the context of the variation under evaluation by the PRAC and CHMP could be considered acceptable provided that satisfactory responses to the request for supplementary information detailed in the adopted assessment report are submitted by the MAH.
- The PRAC considered that 'hepatitis B virus reactivation' should not be added to the RMP as an important identified risk in absence of a proposal for additional pharmacovigilance measures and/or risk minimisation measures.

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

See also Annex I 15.3. **Error! Reference source not found.**

5.3.1. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/II/0126

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to add pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired human immunodeficiency virus (HIV)-1 in adults at high risk. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly

Background

Emtricitabine, a nucleoside analogue of cytidine, with tenofovir disoproxil fumarate, a nucleoside monophosphate analogue of adenosine monophosphate is indicated as antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV)-1 infected adults aged 18 years and over.

The CHMP is evaluating an extension of the therapeutic indication for Truvada, a centrally authorised product containing emtricitabine/tenofovir disoproxil, to include pre-exposure prophylaxis (PrEP), in combination with safer sex practices, to reduce the risk of sexually

acquired HIV-1 in adults at high risk. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see PRAC minutes April 2016.

Summary of advice

- The RMP version 12.0 for Truvada (emtricitabine/tenofovir disoproxil) in the context of the variation under evaluation by the CHMP was considered acceptable provided that satisfactory responses to a request for supplementary information (RSI) are submitted by the MAH.
- The PRAC agreed with the targeted follow-up questionnaire which addresses the safety concerns of HIV-1 infection resulting from non-adherence and drug resistance, aiming at gathering data on patients who seroconvert, including patient characteristics and dosing regimen, and at assisting in identifying potential reasons for failure of prophylaxis. In addition, the PRAC agreed with the proposed pregnancy follow-up, the need to enrol patients in the antiretroviral pregnancy registry (APR), as well as with the proposed drug utilisation study (DUS) consisting of a survey to be sent to prescribers. The MAH should submit to EMA, within 60 days after CHMP opinion, a DUS protocol. With regard to risk minimisation measures (RMM), the PRAC advised some refinements to the prescriber's checklist, safety information for prescribers and patients, as well as to the patient's reminder card.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1. **Error! Reference source not found.**

6.1.1. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201512

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

Background

Afamelanotide, a melanocortin receptor agonist, is indicated for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

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

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. Bimatoprost, timolol - GANFORT (CAP) - PSUSA/00002961/201511 (with RMP)

Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

Background

The combination of bimatoprost, a prostaglandin analogue, with timolol, a beta-blocker, is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ganfort, a centrally authorised medicine containing bimatoprost and timolol, 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 risk-benefit balance of Ganfort (bimatoprost, timolol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information of Ganfort (bottle and preservation free (PF) single dose presentations should be updated to include 'bradycardia', 'hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy', 'eye swelling, 'asthma' as undesirable effects with an unknown frequency. In addition, the product information of Ganfort only should be updated to add 'vision blurred', 'fatigue', 'dysgeusia', 'insomnia', 'nightmare' and 'alopecia' as undesirable effects with an unknown frequency while 'dyspnoea' should be added as an unknown frequency to the product information of Ganfort PF only. Therefore the current terms of the marketing authorisation(s) should be varied[20].
- The MAH should submit to EMA, within 90 days, a variation to update the undesirable effects section of the product information of Ganfort and Ganfort PF in order to align the safety profile, improve clarity and readability and implement the relevant RMP updates.

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. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201512 (with RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

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

Clofarabine, a purine nucleoside anti-metabolite, is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Evoltra, a centrally authorised medicine containing clofarabine, 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 risk-benefit balance of Evoltra (clofarabine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a new warning that renal failure or acute renal failure have been observed as a consequence of infections, sepsis and tumour lysis syndrome, and therefore patients should be monitored for renal toxicity and clofarabine discontinued as necessary. In addition, 'renal failure, acute renal failure' should be added as undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[21].
- In the next PSUR, the MAH should provide a review of cases of off-label use in paediatric patients with acute myeloid leukaemia (AML), in ALL patients with less than two prior regimens, or in combination with other drugs. In addition, the MAH should provide a review of any cases with a fatal outcome and reported adverse drug reactions of death (solicited and unsolicited cases) received during the covering period of the next PSUR.
- The MAH should submit to EMA, within 60 days, a variation to improve the readability of the section of the SmPC on 'special warnings and precautions for use'[22] of the product information by adding relevant subheadings in order to better find the information.

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

6.1.4. Fondaparinux - ARIXTRA (CAP) - PSUSA/00001467/201512

Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Fondaparinux, an antithrombotic agent, is indicated in adults for the prevention of venous thromboembolic events (VTE), treatment of acute deep vein thrombosis (DVT), treatment of acute pulmonary embolism (PE) and treatment of unstable angina or non-ST segment elevation myocardial infarction.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Arixtra, a centrally authorised medicine containing fondaparinux, and issued a recommendation on

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

its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Arixtra (fondaparinux) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'allergic reactions' as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[23].
- In the next PSUR, the MAH should provide a discussion on the need to update the adverse reactions in medical patients as appropriate in light of those already labelled for patients undergoing surgery. In addition, the MAH should provide a detailed review of new cases of pregnancy. Moreover, the MAH should comment on off-label use in France and propose appropriate measures as applicable.

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

6.1.5. Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201512

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

Background

Lenalidomide, an anti-neoplastic, anti-angiogenic and pro-erythropoietic immunomodulator, is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for a transplant, and indicated in combination for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. In addition, lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Finally, lenalomide is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revlimid, a centrally authorised medicine containing lenalidomide, 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 risk-benefit balance of Revlimid (lenalidomide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'acquired haemophilia' as an undesirable effect with an unknown frequency. Therefore the

[23] Update of SmPC section 4.8. The package leaflet is not updated. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

current terms of the marketing authorisation(s) should be varied[24].

- The MAH should submit to EMA, by 19 July 2016, a detailed review of cases of pulmonary hypertension and pulmonary arterial hypertension (PAH). In addition, the MAH should also provide a detailed review of cases of viral reactivation with a specific focus on cases of reactivation of hepatitis B virus (HBV) and varicella-zoster virus (VZV). The need for further product information updates should be considered. The MAH should propose to amend the product information as applicable.
- In the next PSUR, the MAH should provide detailed reviews of cases of leukoencephalopathy and encephalopathy, Guillain-Barre syndrome (GBS), osteonecrosis and osteonecrosis of the jaw, visceral leishmaniasis and propose amendments to the product information as applicable. In addition, the MAH should provide detailed reviews of cases of pulmonary fibrosis, posterior reversible encephalopathy syndrome (PRES), chronic myelogenous leukaemia and graft versus host disease.

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

6.1.6. Liraglutide - SAXENDA (CAP); VICTOZA (CAP) - PSUSA/00001892/201512

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue, is indicated for the treatment of type 2 diabetes mellitus in combination or in monotherapy. It is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult overweight patients when in the presence of at least one weight-related comorbidity or in adult obese patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Saxenda and Victoza, centrally authorised medicine containing liraglutide, 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 risk-benefit balance of Saxenda and Victoza (liraglutide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'increased lipase' and 'increased amylase' as undesirable effects with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied[25].
- In the next PSUR, the MAH should include two drug utilisation studies[26] (DUS)

[24] Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[25] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[26] Study NN8022-4241: In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study

planned for liraglutide and weight management. In addition, the MAH should provide the proportions of use in each of the different off-label indications for liraglutide.

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.

6.1.7. Omalizumab - XOLAIR (CAP) - PSUSA/00002214/201512

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

Background

Omalizumab, a recombinant DNA-derived humanised monoclonal antibody, is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma in the context of a convincing immunoglobulin E (IgE) mediated asthma, and under certain conditions. Omalizumab is also indicated in adults and adolescents for the treatment of chronic spontaneous urticaria as add-on to existing treatment under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xolair, a centrally authorised medicine containing omalizumab, 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 risk-benefit balance of Xolair (omalizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'systemic lupus erythematosus (SLE)' as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[27].
- In the next PSUR, the MAH should provide a further analysis of a reported case of leukaemia. In addition, the MAH should provide a detailed review of events in breastfeeding and propose amendments to the product information as applicable. Finally, the MAH should perform a detailed review of cases of breast cancer and conduct a meta-analysis of clinical trials with appropriate duration.

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

6.1.8. Sofosbuvir - SOVALDI (CAP) - PSUSA/00010134/201512

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

Study NN8022-4246: In market utilisation of liraglutide used for weight management in the UK: a study in the CPRD (Clinical Practice Research Datalink) primary care database

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

Background

Sofosbuvir, a direct-acting antiviral (DAAV) agent, is indicated in adults for the treatment of chronic hepatitis C (CHC) in combination with other medicinal products.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sovaldi, a centrally authorised medicine containing sofosbuvir, 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 risk-benefit balance of Sovaldi (sofosbuvir) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on 'severe bradycardia and heart block' to state that cases have been observed when sofosbuvir is used in combination with another DAAV (including daclatasvir, simeprevir and ledipasvir) and amiodarone, and to state that patients taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. In addition, the sections on 'interaction with other medicinal products and other forms of interaction' and 'undesirable effects' should be updated accordingly. Therefore the current terms of the marketing authorisation(s) should be varied[28].
- In the next PSUR, the MAH should provide a detailed review of psychiatric events with a particular focus on psychotic disorders and worsening of underlying psychiatric conditions with a suggestive chronology and include an analysis of the article by *Lundgren et al*.[29]. In addition, the MAH should provide a detailed review of cases of severe transaminitis, including any reports of hepatic diseases worsening, and should propose amendments to the product information as applicable. Moreover, the MAH should provide detailed reviews of cases suggestive of liver injury in patients concomitantly receiving oestrogen, and cases of bradyarrhythmia with sofosbuvir in the absence of amiodarone, as well as of possible interactions with vitamin K antagonists and changes in international normalised ratio (INR) with sofosbuvir, and should propose amendments to the product information as applicable. Furthermore, the MAH should provide reviews of post-marketing data regarding convulsion/epilepsy events, post-marketing cases of muscular disorders reported in the absence of ribavirin (RBV) or peginterferon (PEG)/RBV co-therapy, or which persisted after the end of antiviral therapy, with an evolution independent of a potential cryoglobulinemia. Finally, the MAH should submit a cumulative analysis of vasculitis events and should provide analysis of any new information relating to the signal of pulmonary arterial hypertension.

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.

[28] Update of SmPC sections 4.4, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

[29] Lundgren et al, Mental health impact of hepatitis C virus (HCV) treatment in human immunodeficiency virus (HIV)/HCV Patients: direct acting antiviral agent (DAA) vs interferon (IFN)-based therapy (Abstract 695). Conference on retroviruses and opportunistic infections (CROI); 2015 23-26 February; Seattle, Washington. p. 306

6.1.9. Umeclidinium bromide, vilanterol - ANORO (CAP); LAVENTAIR (CAP) - PSUSA/00010264/201512

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

Background

The combination of umeclidinium bromide, an inhaled long-acting muscarinic receptor antagonist and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA), is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Anoro and Laventair, centrally authorised medicines containing umeclidinium bromide and vilanterol, and issued a recommendation on its marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Anoro and Laventair (umeclidinium bromide/vilanterol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'urinary retention, dysuria, bladder outlet obstruction' as an undesirable effect with a rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied[30].
- In the next PSUR, the MAH should submit a detailed review of cases of glaucoma including a discussion on the population at risk, and should closely monitor cases of 'urinary retention, dysuria, bladder outlet obstruction' in order to better characterize these in terms of severity and time to onset. The MAH should also update the RMP to delete 'bladder outflow obstruction, urinary retention' from the list of important potential risks.

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

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

See also Annex I 16.2. **Error! Reference source not found.**

6.2.1. Bosentan - STAYVEER (CAP); TRACLEER (CAP); NAP - PSUSA/00000425/201511

Applicant: Marklas Nederlands BV (Stayveer), Actelion Registration Ltd. (Tracleer), various

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

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

Background

Bosentan, an antihypertensive agent blocking the endothelin-1 (ET-1) hormone, is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO[31] functional class III as well as to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tracleer and Stayveer, centrally authorised medicines containing bosentan, and nationally authorised medicines containing bosentan, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of bosentan-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'blurred vision' as a new adverse effect with an unknown frequency as well as a warning regarding an 'effect on ability to drive and use machines'. Therefore the current terms of the marketing authorisations should be varied[32].
- In the next PSUR, the MAHs should provide detailed reviews on 'telangiectasia' including a critical analysis of the publication by *Hetzer S et al.*[33], as well as on the risk of hepatocellular carcinoma (HCC), including a further analysis of epidemiological data on the incidence of HCC in the concerned population together with a discussion on further investigation of the HCC incidence in patients treated with bosentan.

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 procedures including nationally authorised products (NAPs) only

See also Annex I 16.3. **Error! Reference source not found.**

6.3.1. Apomorphine (NAP) - PSUSA/00000227/201511

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

[31] World Health Organization
[32] Update of SmPC section 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[33] Hetzer S, Buhren BA, Schrumpf H, Bolke E, Meller S, Kammers K, Gerber PA, Homey B. European Journal of Medical Research 19: No. 2, 10 Jan 2014 (English). Retrospective analysis of the frequency of centrofacial telangiectasia in systemic sclerosis patients treated with bosentan or ilomedin

Apomorphine, a non-selective dopamine agonist, is indicated for the treatment of motor fluctuations ('on/off' phenomena) in patients with Parkinson's disease (PD) which is not sufficiently controlled by oral anti-Parkinson medication. Apomorphine is also indicated as a pro-emetic for use after acute poisoning, for which fast-onset evacuation of the poison is necessary and lethal outcome or severe complications can be expected.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing apomorphine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of nationally authorised medicinal products containing apomorphine in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include further warnings relating to the adverse reaction of dopamine dysregulation syndrome (DDS) and its risk factors , and to add 'aggression' and 'agitation' as undesirable effects with a unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[34].
- In the next PSUR, the MAHs of apomorphine-containing products indicated in the treatment of PD should provide detailed reviews of cases of 'anxiety', 'psychotic disorder', 'dopamine agonist withdrawal syndrome (DAWS)', 'punding' as well as cases of dopamine dysregulation syndrome (DDS), including an analysis of potential preventive measures. In addition, the MAHs should include a review of impulse control disorders and propose an update of the product information as applicable. Furthermore, the MAHs with a RMP in place should include 'QT prolongation' as an 'important potential risk' in the safety specifications, and 'QT prolongation with combined use of domperidone and apomorphine' as an 'important identified risk' in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP, or at the latest by July 2018. Finally, MAH Britannia should provide further details on the TOLEDO[35] study.

In order to further assess data on DDS, the MAHs should submit to EMA an additional PSUR within 90 days of the data lock point set on 19/11/2016. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is required and the EURD list should be updated accordingly. Following PSURs should be submitted in accordance with the requirements set out in the EURD list.

With regard to domperidone, it was reminded that it is most often used with apomorphine to reduce severe adverse effect such as emesis and vomiting. During the last PSUSA procedure (PSUSA/00000227/201505, see PRAC minutes January 2016), the apomorphine product information was amended to facilitate the safe use of domperidone together with apomorphine, adding a number of warnings and precautions. Nevertheless, the product

[34] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[35] Multicentre, parallel-group, double-blind, placebo controlled phase III study to evaluate the efficacy and safety of apomorphine subcutaneous infusion in Parkinson's disease patients with motor complications not well controlled on medical treatment

information of domperidone still includes information which seems contradictory with the apomorphine product information. Therefore, PRAC agreed a separate list of questions to be addressed by MAHs of domperidone-containing products in the next PSUR single assessment procedure (DLP: 19/11/2016).

6.3.2. Benazepril (NAP) - PSUSA/00000313/201511

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Benazepril, an angiotensin-converting enzyme (ACE) inhibitor, is indicated primarily for the treatment of hypertension, congestive heart failure, and chronic renal insufficiency.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicinal products containing benazepril, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of benazepril-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the interactions of benazepril with cyclosporin and heparin to reflect that hyperkalaemia may occur. In addition, a warning on interaction between benazepril and non-steroidal anti-inflammatory drugs (NSAIDs) should be added to exercise caution when administering these medications simultaneously due to the potential attenuation of the antihypertensive effect as well as a potential increased risk of worsening of renal function and an increase in serum potassium. Moreover, a warning on interaction with mechanistic target of rapamycin (mTOR) inhibitors should be added due to the increased risk of angioedema. Finally, the overdose section should be updated to include that the main expected sign is marked hypotension, which can be associated with electrolyte disturbances and renal failure. Therefore the current terms of the marketing authorisation(s) should be varied[36].
- In the next PSUR, all the MAHs should provide reviews of cases of 'rhabdomyolysis', 'hyperkalaemia' when used concomitantly with trimethoprim or with co-trimoxazole, and the risk of sudden death when used concomitantly with co-trimoxazole.

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. Benzydamine (NAP) - PSUSA/00000375/201510

Applicant: various

[36] Update of SmPC sections 4.5 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Benzydamine is a locally-acting non-steroidal anti-inflammatory drug (NSAID) with local anaesthetic and analgesic properties for pain relief and anti-inflammatory treatment of various inflammatory conditions. At topical concentrations, benzydamine also acts as a mild disinfectant and superficial anaesthetic. It is available in different formulations used in gynaecology and for oral and topical use.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing benzydamine and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of benzydamine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information of oral benzydamine formulations should be updated to include 'hypersensitivity reactions' and 'anaphylactic reactions' as undesirable effects with an unknown frequency. In addition, the product information for all benzydamine formulations except creams for topical use and lozenges should be updated to add information on overdose symptoms. Therefore the current terms of the marketing authorisation(s) should be varied[37].
- In the next PSUR, the MAHs should consider adding 'abuse and related psychiatric effects' as an important identified risk for gynaecological formulations, 'hypersensitivity reactions (including anaphylactic reactions)' as an important identified risk for oral formulations. In addition, MAHs should provide a review of potential cases of incorrect route of drug administration.

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

6.3.4. Dextromethorphan (NAP) - PSUSA/00001009/201511

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

Background

Dextromethorphan, a synthetic morphine derivative, is indicated for the symptomatic treatment of non-productive cough in children and adults. Alone or in combination, dextromethorphan can be used in preparations to treat the symptoms of the common cold.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of

[37] Update of SmPC sections 4.8 and 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

nationally authorised medicines containing dextromethorphan, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of dextromethorphan-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include warnings on possible drug abuse as well as on interaction between dextromethorphan with CYP2D6[38] inhibitors that can increase dextromethorphan concentrations and lead to toxic effects of dextromethorphan and development of serotonin syndrome.Therefore, patients should be monitored and dextromethorphan dose may need to be reduced. Therefore the current terms of the marketing authorisation(s) should be varied[39].
- The PRAC considered that the changes for dextromethorphan-containing products in relation to the metabolism of dextromethorphan and the warning about the possible interaction with cytochrome P450 2D6 (CYP2D6) inhibitors also apply to fixed-dose combination products containing dextromethorphan. Therefore, MAHs for fixed-dose combination should be advised to reflect these amendments to their product information.

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

6.3.5. Furosemide, spironolactone (NAP) - PSUSA/00001493/201512

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Furosemide, a loop diuretic and spironolactone, an aldosterone antagonist, are indicated in combination in the treatment of ascites in patients with liver diseases, pulmonary oedema due to cardiac insufficiency, oedema in patients with nephrotic syndrome, hypertension if accompanied by disturbances in electrolyte balance due to hyperaldosteronism and when previous diuretic therapy has proved inadequate.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing furosemide and spironactolone, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of furosemide/spironolactone-containing medicinal products in the approved

[38] Cytochrome P450 2D6
[39] Update of SmPC sections 4.4, 4.5 and 5.2. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

indications remains unchanged.

- Nevertheless, the product information should be updated to include a warning on the interaction between the spironolactone component with trimethoprim/sulfamethoxazole (co-trimoxazole) leading to severe hyperkalaemia. Therefore the current terms of the marketing authorisation(s) should be varied[40].
- In the next PSUR, MAH Sanofi-Aventis should provide a detailed review on decreased bone mineral density.
- Taking into account the seriousness of the risk of sudden death due to hyperkalaemia, the PRAC considered that the interaction between the spironolactone component and trimethoprim/sulfamethoxazole (co-trimoxazole) also apply to trimethoprim-containing products. Therefore, MAHs for trimethoprim-containing products should be advised to reflect these amendments to their product information.

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

6.3.6. Minoxidil (topical formulation) (NAP) - PSUSA/00002067/201510

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

Background

Minoxidil, a potassium channel opener, is indicated as a topical formation for the treatment of androgenetic alopecia in men and women.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing minoxidil (topical formulation), and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of minoxidil-containing medicinal products (topical formulation) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include allergic reactions including angioedema as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[41].
- In the next PSUR, the MAHs should provide a detailed review of cases associated with accidental ingestion of topical minoxidil including an evaluation of the adequacy of existing risk minimisation measures. In addition, the MAHs (McNeil, Johnson & Johnson, Bio-H-Tin Pharma, Galderma, Laboratoire Bailleul, A Menarini, Pierre Fabre,

[40] Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position
[41] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Sandoz, Laboratoire Gifrer) should provide a review of the use of the 5% cutaneous solution, particularly focussing on hypertrichosis and should propose to update the product information as appropriate. Finally, the MAHs McNeil and Johnson & Johnson should provide a detailed review of cases of anaphylaxis and medication errors.

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

6.3.7. Technetium (^{99m}Tc) mebrofenin (NAP) - PSUSA/00002861/201511

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Technetium (^{99m}Tc) mebrofenin is a diagnostic radiopharmaceutical for the hepatic and reticulo-endothelial systems indicated for hepatobiliary imaging and hepatobiliary function studies.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing technetium (^{99m}Tc) mebrofenin, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of technetium (^{99m}Tc) mebrofenin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the potential for hypersensitivity or anaphylactic reactions and 'hypersensitivity' should be added as undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied[42].

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

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4. **Error! Reference source not found.**

6.4.1. Ingenol mebutate - PICATO (CAP) - EMEA/H/C/002275/LEG 008

Applicant: Leo Pharma A/S

PRAC Rapporteur: Julie Williams

[42] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Scope: Following PSUSA/00010035/201507, submission of a review relating to study LP0105-1020[43] (efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis)

Background

Ingenol mebutate induces local lesion cell death and promotes an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. It is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

Following the evaluation of the most recently submitted PSUR for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see PRAC minutes February 2016). 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[44] to update the product information with the results of study LP105-1020[45]. In addition, the MAH should discuss further proposals for non-clinical studies which could provide evidence to support their proposed mechanism, provide a proposal and timeline for reassessment of histology data from LP0105-1020 and in light of the limitations of study LP0041-63[46], the MAH should make a proposal for a further study to investigate the issue of the increase in incidence of progression of actinic keratosis (AK) to squamous cell carcinoma (SCC).

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[47]

See also Annex I 17.1. **Error! Reference source not found.**

7.1.1. Eliglustat - CERDELGA (CAP) - EMEA/H/C/PSP/0047

Applicant: Genzyme Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS protocol for registry study OBS14099: a prospective, multicentre, observational post authorisation safety sub-registry to characterize the long-term safety profile of eliglustat of adult patients with Gaucher disease

Background

[43] Efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis. NCT01998984.
[44] Update of SmPC sections 4.4 and 5.1.
[45] An international, phase 2, randomised, multicentre, double-blind, vehicle-controlled, 8-week trial: efficacy and safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm^2 on trunk and extremities in subjects with actinic keratosis
[46] A Phase 4 trial comparing the cumulative incidence of squamous cell carcinoma (SCC) after treatment with ingenol mebutate and imiquimod for multiple actinic keratoses on face and scalp. A multi-centre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial. EudraCT number: 2012-003112-31. nct01926496
[47] In accordance with Article 107n of Directive 2001/83/EC

Cerdelga is a centrally authorised medicine containing eliglustat indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1), who are CYP2D6[48] poor metabolisers (PMs), intermediate metabolisers (IMs) or extensive metabolisers (EMs).

A protocol for a non-interventional PASS was submitted to PRAC in accordance with the conditions to the marketing authorisation(s) to characterize the long-term safety profile of eliglustat in adult patients suffering from Gaucher disease.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 2.0 in accordance with Article 107n of Directive 2001/83/EC, objected to it for the above listed medicinal product(s), as the Committee considered that at this stage, the design of the study did not fulfil the study objectives. The MAH should further clarify aspects relating to the study milestones, setting, variables, data analysis, limitations of the research methods and the plans for disseminating and communicating the study results.
- The MAH should submit to EMA, within 60 days, a revised PASS protocol. A 60 days assessment timetable will be applied.

7.1.2. Glycerol phenylbutyrate - RAVICTI (CAP) - EMEA/H/C/PSP/0048

Applicant: Horizon Pharma Ireland Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: PASS protocol for a multicentre prospective non-interventional registry in patients with urea cycle disorders on treatment with glycerol phenylbutyrate to characterise patients' demographics, and to document long-term safety and clinical outcomes

Background

Ravicti is a centrally authorised medicine containing glycerol phenylbutyrate indicated for use as adjunctive therapy for chronic management of adult and paediatric patients aged 2 months or more with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

A protocol for a non-interventional PASS was submitted to PRAC in accordance with the conditions to the marketing authorisation(s) to characterize the long-term safety profile of glycerol phenylbutyrate.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to it for the above listed medicinal product(s), as the Committee considered that at this stage, the design of the study did not fulfil the study objectives. The MAH should further clarify aspects relating to the study milestones, research question and objectives, study design, data management, quality control, protection of human subjects, management and

[48] cytochrome P450 2D6

reporting of adverse events/adverse reactions and plans for disseminating and communicating the study results.

- The MAH should submit to EMA, within 60 days, a revised PASS protocol. A 60 days assessment timetable will be applied.

7.1.3. Levofloxacin - QUINSAIR (CAP) - EMEA/H/C/PSP/0049

Applicant: Raptor Pharmaceuticals Europe BV

PRAC Rapporteur: Dolores Montero Corominas

Scope: PASS protocol for an open-label, observational safety study of Quinsair (nebulised levofloxacin hemihydrate) in patients with cystic fibrosis and chronic *Pseudomonas Aeruginosa* infection, using data collected through European cystic fibrosis registries.

Background

Quinsair is a centrally authorised medicine containing levofloxacin indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis.

A protocol for a non-interventional PASS was submitted to PRAC to characterize the long-term safety profile of levofloxacin in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection through collection of safety data from European cystic fibrosis registries during a 5-year study by the MAH.

Endorsement/Refusal of the protocol

- The PRAC, having considered the draft protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to it for the above listed medicinal product(s), as the Committee considered that at this stage, the design of the study did not fulfil the study objectives. A number of concerns regarding the milestones, the study objectives, study design, setting, variables, data source, study size, data management and analysis, quality control, protection of human subjects, management and reporting of adverse events/adverse reactions and plans for disseminating and communicating the study results were raised by the Committee.
- The PRAC therefore recommended that the MAH should submit a revised PASS protocol within 60 days to EMA. A 60 days assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[49]

See also Annex I 17.2. **Error! Reference source not found.**

7.2.1. Hydrocortisone - PLENADREN (CAP) - EMEA/H/C/002185/MEA 005.3

Applicant: Shire Services BVBA

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's responses to MEA 005.2 revised PASS protocol for study SWE-DUS, study 10918 -404 (SHP617-404): a Swedish retrospective study, progress reports to be provided

[49] 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

on a yearly basis, as part of the PSURs, evaluating the pattern of Plenadren use from Swedish quality registries as per the request for supplementary information (RSI) adopted by PRAC in February 2016

Background

Plenadren is a centrally authorised medicine containing hydrocortisone, a glucocorticoid for systemic use, used in the treatment of adrenal insufficiency in adults.

As part of the RMP for Plenadren, the MAH was requested to conduct a study (SWE-DUS[50]) to monitor off-label use of Plenadren and to evaluate physicians' prescribing patterns with progress reports to be provided on a yearly basis as part of the PSURs. Nevertheless, a question was raised on study feasibility, further to the slow progress of the study and issues related to data extraction. The PRAC was requested to provide advice to CHMP on the MAH's proposal not to further pursue the study. For further background, see PRAC minutes February 2014, PRAC minutes September 2015 and PRAC minutes February 2016.

Summary of advice

- Although the study objectives have not been fulfilled as the data requested were not provided, and given that off label use is closely monitored in PSURs, the PRAC considered the MAH's proposal acceptable without further action warranted.

7.3. Results of PASS imposed in the marketing authorisation(s)[51]

7.3.1. Cyproterone, ethinylestradiol (NAP) – EMEA/H/N/PSR/J/005

Applicant: Bayer Pharma AG, various

PRAC Rapporteur: Menno van der Elst

Scope: Final study results for an imposed joint PASS: drug utilisation study (DUS) (survey) for cyproterone/ethinyl estradiol to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess the main reasons for prescription

Menno van der Elst was appointed as Rapporteur for the procedure.

7.4. Results of PASS non-imposed in the marketing authorisation(s)[52]

See Annex I 17.4.

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

See Annex I 17.5. **Error! Reference source not found.**

7.6. Others

See Annex I 17.6.

[50] A Swedish, retrospective study evaluating the pattern of Plenadren use from Swedish quality registries
[51] In accordance with Article 107p-q of Directive 2001/83/EC
[52] 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

7.7. 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.

7.8. Ongoing 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.

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I.18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I.18.2.

8.3. Renewals of the marketing authorisation

See Annex I.18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

10. Other safety issues for discussion requested by the 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

10.3.1. Dapagliflozin – EDISTRIDE (CAP) - EMEA/H/C/004161/LEG 001.1; FORXIGA (CAP) - EMEA/H/C/002322/LEG 019.1 dapagliflozin, metformin – EBYMECT (CAP) - EMEA/H/C/004162/LEG 001.1; XIGDUO (CAP) - EMEA/H/C/002672/LEG 005.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: PRAC consultation on the assessment of the risk of toe amputation with dapagliflozin-containing medicines in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicines

Background

Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

Following the initiation in April 2016 of a referral procedure under Article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicines on the risk of lower limb amputation primarily of the toe, observed in ongoing clinical trials, a list of questions was addressed to the MAH of dapagliflozin-containing medicines in order to further investigate any possible evidence of an increased risk of lower limb amputation associated with other medicinal products of the SGLT2 inhibitors class as well. For further background, see PRAC minutes April 2016 and PRAC minutes June 2016. At the current meeting, the PRAC discussed the MAH's responses to request for supplementary information (RSI) and their assessment.

Summary of advice

- Based on the available data, the PRAC considered that a class effect could not be excluded in light of the current evidence. As a result, in response to the request of the European Commission, the PRAC considered by majority that the review under Article 20 of Regulation (EC) No 726/2004 of canagliflozin-containing medicines should be broadened to the whole class of SGLT2-inhibitors to allow a review of data on the risk of amputation, including reports from post-marketing and any other sources, and their impact on the benefit-risk balance of authorised SGLT2-inhibitor medicines. See 3.2.3.

10.3.2. Empagliflozin – JARDIANCE (CAP) - EMEA/H/C/002677/LEG 006 empagliflozin, metformin – SYNJARDY (CAP) - EMEA/H/C/003770/LEG 004

Applicant: Boehringer Ingelheim GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: PRAC consultation on the assessment of the risk of toe amputation with empagliflozin-containing medicines in the context of the ongoing article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing medicines

Background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated alone or in combination with metformin, a biguanide, for the treatment in adults with type 2 diabetes mellitus to improve glycaemic control under certain conditions.

Following the initiation in April 2016 of a referral procedure under Article 20 of Regulation (EC) No 726/2004 for canagliflozin-containing products on the risk of lower limb amputation primarily of the toe, observed in ongoing clinical trials, a list of questions was addressed to the MAH of empagliflozin-containing products in order to further investigate any possible evidence of an increased risk of lower limb amputation associated with other medicinal products of the SGLT2 inhibitors class. For further background, see PRAC minutes April 2016 and PRAC minutes June 2016.

Summary of advice

- Based on the available data, the PRAC considered that that a class effect could not be excluded in light of the current evidence. As a result, in response to the request of the European Commission, the PRAC considered by majority that the review under Article 20 of Regulation (EC) No 726/2004 of canagliflozin-containing medicines should be broadened to the whole class of SGLT2-inhibitors to allow a review of data on the risk of amputation, including reports from post-marketing and any other sources, and their impact on the benefit-risk balance of authorised SGLT2-inhibitor medicines. See 3.2.3.

10.4. 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.

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

11.2.1. Valproate and related substances: sodium valproate, valproic acid, valproate semisodium, valpromide (NAP)

Applicant: Sanofi, various

PRAC Lead: Sabine Straus

Scope: PRAC consultation on the need for a box warning on outer package and patient alert card in addition to risk minimisation measures adopted as an outcome of the completed referral procedure under Article 31 referral of Directive 2001/83/EC

Background

Valproic acid, an acidic organic compound, as well as valproate and its related salts and esters, are indicated for the treatment of generalised, partial or other epilepsy, and for the treatment of manic episodes under certain conditions. Valproate is also indicated to prevent migraine headaches in some EU Member States.

In October 2014, the PRAC concluded a safety referral procedure under Article 31 of Directive 2001/83/EC for valproate and related substances and recommended strengthening restrictions on the use of valproate and related substances in women and girls, due to the risk of malformations and neurodevelopmental disorders in children exposed to valproate in the womb (EMA/686022/2014). The PRAC also recommended that educational material (including a prescriber guide and patient booklet) was needed to improve healthcare professionals' awareness of the risks regarding pregnancy outcomes and to ensure that female patients are informed of, and understand, the risks associated with valproate use during pregnancy, the need to use effective contraception and the need for regular review of treatment, as well as the need to consult the prescriber if she is planning a pregnancy or becomes pregnant. For further background, see PRAC minutes October 2014.

In May 2016, the CMDh discussed a letter from the MAH of the originator-medicinal product containing valproate including an overview on the implementation status of the risk minimisation measures (RMM) agreed in the concluded safety referral, and proposing to harmonise in the EU further additional risk minimisation measures. Various MSs have requested at national level measures that were additional to the set of risk minimisation measures agreed in the referral. These include for example an outer package warning, a patient alert card (PAC) and/or a pictogram on the outer packaging. For further background, see CMDh minutes May 2016. At the current PRAC meeting, the Netherlands requested PRAC advice on the implementation of these further additional RMM and sought advice on the proposal from the MAH of the originator medicinal product.

Summary of advice

- Based on the review of the available information and initiatives undertaken in several Member States, the PRAC emphasized that communication between healthcare professionals (HCP) and patients is key to conveying the risks of valproate-containing medicines in pregnancy. For this reason, the PRAC stressed the importance of the statutory tools and the additional risk minimisation measures agreed during the Article 31 referral procedure in 2014 (EMA/612389/2014).
- Alongside the implementation of the additional risk minimisation activities, the PRAC acknowledged that complementary measures and tools might be required at national

level to communicate the risk of neurodevelopmental disorders and congenital malformations in children exposed to valproate in the womb. Considering the specificities in Member States, such as the usage pattern of valproate-containing medicines and characteristics of the healthcare delivery system, further additional risk minimisation measures could be taken as appropriate.

- Without prejudice to the above, the PRAC also discussed the findings of recent studies on communication to HCPs and their awareness of the information, on patients' understanding of pictograms, and the current practices on valproate risk communication. The PRAC acknowledged the role of NCAs in evaluating the effectiveness of further additional risk minimisation measures for female patient awareness and education and their adequacy depending on the national understanding of such measures.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh

None

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

12.3.1. CHMP guideline on influenza vaccines

The EMA Secretariat presented to PRAC the draft updated guideline on influenza vaccines following public consultation and agreed by the Vaccine Working Party (VWP). The PRAC adopted the guideline. As a next step, PDCO is to be consulted before final adoption at CHMP in July 2016.

Post-meeting note: On 29 July 2016, the 'Guideline on Influenza Vaccines, Non-clinical and Clinical Module' (EMA/CHMP/VWP/457259/2014) was published on the EMA website following adoption at the July 2016 CHMP plenary meeting.

12.3.2. Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMP) - revision

PRAC lead: Julie Williams, Brigitte Keller-Stanislawski

As a follow-up to the last PRAC discussions on the exercise to revise the 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' (EMEA/149995/2008) (see PRAC minutes January 2016 and PRAC minutes April 2016), the EMA Secretariat presented to PRAC a progress update from the drafting group, composed of CAT, CHMP, PRAC and EMA members. A further update will be given in due course.

12.3.3. Scientific Advice Working Party (SAWP) – consultation procedure: criteria

As agreed at the last PRAC discussion on the proposed approach for PRAC consultation on scientific advice outside the ongoing pilot for non-imposed post-authorisation studies (see PRAC minutes March 2016) and in line with the PRAC work plan 2016, the EMA secretariat presented to PRAC, following two break out-sessions with PRAC delegates in the margins of previous PRAC plenary meetings, a process and set of criteria to involve PRAC in the scientific advice procedure when pharmacovigilance (e.g. RMP and PASS planning) questions are posed, based on the experience gained so far. Further discussion is scheduled in September/October 2016 on revised draft criteria.

12.4. Cooperation within the EU regulatory network

12.4.1. Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE)

At the organisational matters teleconference held on 21 July 2016, the PRAC was further updated on the SCOPE Joint Action project initiated by the European Commission following the implementation of the revised EU pharmacovigilance legislation in 2012 to help medicines regulators to operate pharmacovigilance systems to the EU legislative requirements (see PRAC minutes March 2016). A status update on the progress made by the eight Work Packages (WP)[53] was presented with their deliverables and timelines together with an overall sustainability plan (including a 6-month extension of the project until April 2017). An overview was presented of the pilot trainings held in May and June 2016 to gain feedback on selected training topics and format, and in preparation for the main trainings in September and October 2016. The PRAC welcomed receiving regular updates on the progress of SCOPE.

12.5. Cooperation with International Regulators

None

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

None

12.7. PRAC work plan

12.7.1. 2016 PRAC work plan – status update

The EMA Secretariat presented to the PRAC a mid-year status update on the activities described in the PRAC work plan 2016. A report shall be prepared for the end of the year.

[53] WP1: Governance; WP2: Dissemination; WP3: Evaluation; WP4: ADR collection; WP5: Signal management; WP6: Risk communications; WP7: Quality management systems; WP8: Lifecycle pharmacovigilance

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system - PRAC work tracking including quarterly workload measures and performance indicators for the last three months - predictions

At the organisational matters teleconference held on 21 July 2016, as part of the revised governance of the EU pharmacovigilance move to full operation that requires oversight of performance of the EU system and measuring its impact (see PRAC minutes April 2016), the EMA secretariat presented quarterly figures on EU pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, when available, and per NCA, for the upcoming months.

12.8.2. Marketing Authorisation Applications - planned for the remainder of 2016

The EMA Secretariat presented to the PRAC for information a report on marketing authorisation applications planned for submission (business pipeline) before the end of 2016. The PRAC was informed that this information is presented in a new format, using quarterly reports on expected initial MAAs and horizon planning on a longer time period.

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)

PRAC lead: Menno van der Elst, Margarida Guimarães

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and welcomed the progress being made.

12.10.3. PSURs repository

None

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

The PRAC endorsed the draft revised EURD list version July 2016 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC minutes April 2013).

Post-meeting note: following the PRAC meeting in July 2016, the updated EURD list was adopted by the CHMP and CMDh at their July 2016 meetings and published on the EMA website on 28/07/2016, 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: Sabine Straus

At the organisational matters teleconference held on 21 July 2016, the PRAC was updated on the outcome of the July 2016 SMART Working Group (SMART WG) work stream WS1. The SMART WG WS1 discussed the recording and reporting of non-related adverse events in individual case safety reports (ICSRs) following pharmacovigilance inspectors' observation of variability of coding adverse events (AEs) from organised data collection systems (non-interventional post-authorisation studies, Patient Support Programmes (PSP), and registries). Following consultation with the MSs, further guidance will be developed. In addition, the WG WS1 discussed the signal management work undertaken in SCOPE and the best practice guide as well as trainings from Work Package 5 (WP5) on signal management (see also 12.4.1.). Furthermore, the WG WS1 discussed the experience gained so far with PRAC adoption of signal recommendations outside plenary meetings in line with the criteria developed and Best practice guidance on using PRAC plenary time efficiently (see PRAC minutes May 2016).

12.12. Adverse drug reactions reporting and additional reporting

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

The 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 27/07/2016 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.15. 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 hearings – Dry run

As per the preparation for a dry run in previous PRAC meetings (see PRAC minutes June 2016), the PRAC together with the EMA Secretariat conducted an internal practice exercise (dry run) within the framework of the current PRAC meeting in order to test the process and procedures for public hearings by using a fictional scenario of a safety review. This enabled EMA to ensure all practical arrangements needed for these hearings are in place and PRAC

members to test this new form of interaction. Contributions made by the public during these hearings will be considered by the PRAC and inform the Committee's decision-making. Public hearings will be held on a case-by-case basis as part of referral procedures, where the Committee determines that collecting the views of the public would bring added value to its review in line with the 'Rules of procedure on the organisation and conduct of public hearings at the Pharmacovigilance Risk Assessment Committee (PRAC)' (EMA/363479/2015). The lessons learnt from the dry run will be presented to PRAC in September 2016.

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.19.2. Withdrawn products - Update on the handling of notifications

At the organisational matters teleconference held on 21 July 2016, the EMA secretariat presented to the PRAC an update on the process for handling withdrawn product notifications (WP) in place since 2013 under Article 23a of Directive 2001/83/EC and Articles 13 and 14b of Regulation Regulation (EC) No 726/2004. The process of using a dedicated email address for submitting a notification to EMA and the way information is channelled to Member States was described, together with relevant figures on notifications received so far. A dedicated EMA webpage on withdrawn-product notification: questions and answers provides further details on the process.

12.20. Others

12.20.1. Effects tables in selected important benefit/risk reviews - Pilot phase

PRAC lead: Rafe Suvarna

In line with the PRAC work plan 2016 and based on the CHMP experience, the PRAC was presented with the first effects-table of the pilot that was recently initiated to explore their utility in post-authorisation procedures. This first effects table was constructed using data from a recent referral procedure. The PRAC welcomed the initiative and encouraged further similar exercises using data from selected important benefit-risk reviews as part of the pilot exercise at the level of the PRAC.

12.20.2. EMA hosted industry platform on the operation of the EU pharmacovigilance legislation - Report from quarterly meeting on 01 July 2016

The EMA secretariat reported to PRAC on the Eighth Industry Platform meeting on the operation of pharmacovigilance legislation held on 1 July 2016. The Industry Platform is held on a three-monthly basis. Discussions at the meeting focussed on RMP guidance and templates, the EudraVigilance system, medical literature monitoring (MLM),

pharmacovigilance system master file (PSMF), clinical trials reference safety information (FSI), ISO[54]-IDMP[55] – pharmacovigilance interface, as well as falsification of medicines.

12.20.3. Strategy on measuring the impact of pharmacovigilance - draft reflection paper on PRAC criteria to prioritise collaborative impact research

PRAC lead: Marie Louise (Marieke) De Bruin

Following the last discussion on the 'PRAC strategy on measuring the impact of pharmacovigilance activities' (EMA/790863/2015) (see PRAC minutes May 2016) and in line with the PRAC work plan 2016, the EMA Secretariat, on behalf of the PRAC Interest Group (IG), presented to the PRAC a draft reflection paper on criteria to prioritise collaborative impact research with the purpose of informing the further development and practical application of such criteria. Following discussion and the need for some refinements of the reflection paper, a revised document will be prepared for PRAC adoption in September 2016.

12.20.4. Type II variations - procedural timetables

The EMA secretariat presented to the PRAC a proposal for an alternative procedural timetable for type II variations involving the PRAC, giving a longer assessment time on the 60-day timetable, providing more flexibility when PRAC plenary discussions are needed as well as allowing for a better spread of assessment workload in a calendar month. The PRAC agreed with the proposal. Following discussion at CHMP, EMA secretariat plans to roll out the new alternative timetable during Q4 2016.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation[56]

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria under evaluation for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables[57].

14.1.1. Aripiprazole – ABILIFY (CAP), ABILIFY MAINTENA (CAP)

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Leonor Chambel

[54] International Organization for Standardization
[55] identification of medicinal products
[56] 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
[57] Either MAH's submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

Scope: Signal of compulsive shopping

EPITT 18683 – New signal

Lead Member States: PT, SE

14.1.2. Ipilimumab – YERVOY (CAP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: Signal of type 1 diabetes mellitus

EPITT 18674 – New signal

Lead Member State: NL

14.2. New signals detected from other sources

14.2.1. Exenatide – BYETTA (CAP), BYDUREON (CAP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia

EPITT 18688 – New signal

Lead Member State: SE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the 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. Enoxaparin sodium - EMEA/H/C/004264; EMEA/H/C/003795

Scope: Prophylaxis of thromboembolic disorders of venous origin

15.1.2. Ivabradine - EMEA/H/C/004117

Scope: Treatment of angina pectoris

15.1.3. Parathyroid hormone - EMEA/H/C/003861, Orphan

Applicant: NPS Pharma Holdings Limited

Scope: Treatment of hypoparathyroidism

15.1.4. Sildenafil - EMEA/H/C/004186

Scope: Treatment of pulmonary arterial hypertension

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

As per agreed criteria, the 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. Abacavir - ZIAGEN(CAP) - EMEA/H/C/000252/WS0956/0097/G; abacavir, lamivudine - KIVEXA(CAP) - EMEA/H/C/000581/WS0956/0070/G; abacavir, lamivudine, zidovudine - TRIZIVIR(CAP) - EMEA/H/C/000338/WS0956/0102/G;

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Update of the RMPs for abacavir (ABC)-containing products (Ziagen RMP (version 14); Kivexa RMP (version 6); Trizivir RMP (version 3)), specifically the educational material (slide set) has been streamlined to ensure key messages are clear and that the information is consistent with recent updates to the ABC hypersensitivity reactions language in the SmPC made as part of WS/0733. Annex IID of the product information has been updated accordingly. In addition, the MAH took the opportunity to update the RMP with the recently approved 'class label' variations on lipodystrophy, lactic acidosis and latest mitochondria information

15.2.2. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/II/0026

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: Submission of a revised RMP (version 7) in order to include the outcome of the evaluation from WS/689 (PML added as an important identified risk). The draft PASS protocol for category 3 study 109MS419 (a retrospective, multicentre, observational study to assess the effect of Tecfidera delayed-release capsules on lymphocyte subsets in subjects with relapsing forms of multiple sclerosis) was also submitted. In addition, a discussion on the overall totality of the non-clinical and clinical work being undertaken to further understand lymphopenia associated with Tecfidera treatment is included

15.2.3. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/II/0026/G

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Julie Williams

Scope: Update of Annex IID and of the RMP in order to update the educational material (slide set) and website. Furthermore, the MAH took the opportunity to align the information of the RMP with the recently approved changes to the product information concerning information on lactic acidosis and lipodystrophy

15.2.4. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0039

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of a revised RMP (version 14) including updates on data exposure, medication error cases and effectiveness of risk minimisations measures related to the potential risk of air/gas embolism associated with spray application

15.2.5. Ibandronic acid – BONDRONAT (CAP) - EMEA/H/C/000101/WS0942/0074; BONVIVA (CAP) - EMEA/H/C/000501/WS0942/0056

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of a revised RMP to implement the patient reminder card as an additional risk minimisation measure following the PRAC recommendation provided in PSUSA/001702/201506

15.2.6. Naltrexone, bupropion - MYSIMBA (CAP) - EMEA/H/C/003687/II/0005/G

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of amended study designs for both the renal impairment study (effect of renal impairment on the pharmacokinetics of naltrexone PR/ bupropion PR tablet (category 3 study)) and the hepatic impairment study (effect of hepatic impairment on the pharmacokinetics of naltrexone PR /bupropion PR tablet (category 3 study)) as outlined in the currently approved RMP (version 8)

15.2.7. Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0083

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of a revised RMP (version 15) in order to add hepatitis B reactivation as a new important identified risk

15.2.8. Retigabine - TROBALT (CAP) - EMEA/H/C/001245/II/0044

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: Submission of a revised RMP (version 17) in order to delete category 3 post-authorisation study (PASS) WEUKSTV4551 exploring the risk of urinary retention (UR) among patients treated with retigabine and other antiepileptic drugs (AEDs)

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

As per agreed criteria, the 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. 5-aminolevulinic acid – AMELUZ (CAP) - EMEA/H/C/002204/II/0020

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2) and of field cancerisation based on the phase III clinical study ALA-AK-CT007. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

15.3.2. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS0948/0096; abacavir, lamivudine – KIVEXA (CAP) - EMEA/H/C/000581/WS0948/0069; abacavir, dolutegravir, lamivudine – TRIUMEQ (CAP) - EMEA/H/C/002754/WS0948/0027;

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Claire Ferard

Scope: Update of sections 4.4 and 4.5 of the SmPC to remove the current information regarding a potential interaction between abacavir and ribavirin. The Package Leaflet has been updated accordingly. In addition, the RMPs (Ziagen RMP (version 13); Kivexa RMP (version 5); Triumeq RMP (version 10)) were updated accordingly

15.3.3. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/II/0097

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Extension of indication in combination with methotrexate (MTX) in the treatment of adults with rheumatoid arthritis (RA) who have highly active disease with poor prognostic factors not previously treated with MTX. As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on results from the AVERT study (IM101226). The Package Leaflet and the RMP (version 20) are updated accordingly

15.3.4. Ceritinib - ZYKADIA (CAP) - EMEA/H/C/003819/II/0006/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC based on the final results of the clinical pharmacology study CLDK378A2113 and results of a sub-group evaluating the impact of gastric pH-elevating agents on the steady-state pharmacokinetic (PK), efficacy, and safety of ceritinib in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) patients. The final clinical study report for study CLDK378A2113 is submitted to fulfil MEA 003. In addition, the MAH is proposing a change to the due date for the provision of the final

study report for study CLDK378A2110 (MEA 001). The RMP is updated (version 3.0) accordingly

15.3.5. Crizotinib - XALKORI (CAP) - EMEA/H/C/002489/II/0039

Applicant: Pfizer Limited

PRAC Rapporteur: Claire Ferard

Scope: Extension of indication to include the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) based on the results of study A8081001 (a multinational, multicentre, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC, the Package Leaflet and RMP (version 7.0) are updated accordingly

15.3.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0012

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information to reflect findings from a recently completed phase 3b study (study H9X-MC-GBDG (GBDG)) concerning the use of dulaglutide in combination with sulphonylurea alone. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.7. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0013

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.2, 4.7, 4.8 and 5.1 of the SmPC for Trulicity following completion of a phase 3b study (study H9X-MCGBDI (GBDI)) to reflect the study's findings concerning the use of dulaglutide in combination with basal insulin. The Package Leaflet is updated accordingly

15.3.8. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0032

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the SmPC section 4.4 and 4.8 with new information on the drug-induced liver injury. Consequently, the section of the Annex II on 'key elements to be included in the educational material' has been updated. The RMP (version 39) is updated accordingly

15.3.9. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0035/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the clinical study report (CSR) for study TRC112765 exploring the safety of eltrombopag in subjects with solid tumours receiving gemcitabine monotherapy or gemcitabine plus cisplatin or carboplatin. The RMP (version 40) is updated accordingly. In addition, the MAH took the opportunity to revise due dates for submission of final reports for two studies in the pharmacovigilance plan

15.3.10. Empagliflozin - JARDIANCE(CAP) - EMEA/H/C/002677/WS0926/0017; empagliflozin, metformin - SYNJARDY(CAP) - EMEA/H/C/003770/WS0926/0016

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to include data from study 1275.9. In addition, the MAH took the opportunity to remove the optional sentence on 'medicinal product subject to medical prescription' from Annex IIIA. Moreover, the RMPs (version 8.0 for Jardiance; version 6.0 for Synjardy) are updated accordingly

15.3.11. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/X/0029

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Line extension to add new pharmaceutical form and strengths (film-coated tablets 40 mg and 80 mg) to the currently approved presentations for Xtandi

15.3.12. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/II/0053

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include the use of Zebinix as monotherapy in adults, in addition to the previously authorised indication as adjunctive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 15.0) are updated accordingly

15.3.13. Eslicarbazepine acetate - ZEBINIX (CAP) - EMEA/H/C/000988/X/0050/G

Applicant: Bial - Portela & Cª, S.A.

PRAC Rapporteur: Martin Huber

Scope: Grouping of a line extension application to add a new pharmaceutical form (50 mg/ml oral suspension) and a type II variation (new indication) to add the treatment of children aged 2 years and older. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC, the Package Leaflet and the RMP (version 14.0) are updated accordingly

15.3.14. Fosaprepitant - IVEMEND (CAP) - EMEA/H/C/000743/II/0031

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to include data from the clinical study P031. In addition, the MAH took the opportunity to bring the product information in line with the QRD template (version 9.1). Furthermore, the MAH took the opportunity to align section 4.4 of the SmPC (and Package leaflet respectively) for fosaprepitant (Ivemend) with the changes approved through procedure EMEA/H/C/000527/X/0049/G for aprepitant (Emend). Moreover, the RMP (version 4.0) is updated accordingly

15.3.15. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/II/0024

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.8 of the SmPC to add an appropriate warning relating to interstitial lung disease (ILD) as well as ILD as a post-marketing adverse drug reaction. In addition, the MAH took the opportunity to bring the product information in line with the revised QRD template. The RMP is updated accordingly

15.3.16. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/II/0051/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Claire Ferard

Scope: Grouped variations to introduce an additional nebulizer 'FOX Bavent' for application of Ventavis 10 µg/ mL and Ventavis 20 µg/mL solution, a change of pack sizes within the range of current approved pack sizes as well as consequential changes to SmPC sections 4.2, 4.4, 6.5 and 8, to the labelling and Package Leaflet. In addition, the MAH took the opportunity to delete reference in the product information to nebulizers which are no longer available by the device manufacturer (ProDose and HaloLite), to merge the texts for Ventavis 10 µg/ mL and Ventavis 20 µg/ mL,nebulizer solution into one SmPC and one Package Leaflet text, to update the list of local representatives in the Package Leaflet, to implement minor editorial changes in the annexes and to bring the annexes in line with the latest QRD template version 9.1. The RMP (version 7.0) is updated accordingly

15.3.17. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0053

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 5.1 of the SmPC to include new booster and persistence data with a follow-up of up to 5 years after vaccination with MenACWY-TT. The RMP (version 7.0) is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC

15.3.18. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0006[58]

Applicant: Boehringer Ingelheim International GmbH

[58] Adoption via written procedure and transmission to the CHMP for adoption of an opinion

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Update of sections 4.2 and 4.4 of the SmPC to revise dose recommendations for patients with mild hepatic impairment, based on pharmacokinetic (PK)/pharmacodynamic (PD) modelling data. In addition, the MAH took the opportunity to bring the Annex II in line with the latest QRD template (version 10)

15.3.19. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0122

Applicant: Roche Registration Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Update of section 5.1 of the SmPC and RMP to reflect the results of the IRIS study (study NV20237): a prospective, multicentre, information-gathering study, comprising virological surveillance and assessment of clinical outcomes, which enrolled patients over a 7-year period. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template version

15.3.20. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0027

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include recommendations for dose modifications in case of hepatic toxicity during the treatment, and to include a reduced starting dose of 30 mg for patients with hepatic impairment. The Package Leaflet is updated accordingly

15.3.21. Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0032/G

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 of the SmPC based on data from ongoing study AP24534-07-101 with a median duration of follow-up of approximately 48 months for the CP-chronic myeloid leukaemia (CML) patients and 3.6 months for the advanced phase Ph+ leukemia patients, as well as 48-month follow-up data from the ongoing study AP24534-10-201 (PACE). The Package Leaflet and the RMP (version 14) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and to align the annexes with the latest QRD template (version 10)

15.3.22. Radium (^{223}Ra) - XOFIGO (CAP) - EMEA/H/C/002653/II/0014/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Rafe Suvarna

Scope: 1) Submission of clinical study report for study BC1-06, 'a double-blind, randomized, multiple dose, phase III, multicentre study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases' (MEA 001) 2) Submission of clinical study report for study 15995 'Radium-223 dichloride in castration-resistant (hormone-refractory) prostate cancer patients with bone metastases',

an early access clinical trial in the USA. (MEA 002) 3) Submission of a clinical study report (based on primary completion) for study 16216 'Radium-223 dichloride in castration-resistant (hormone-refractory) prostate cancer patients with bone metastases' an early access clinical trial outside USA. (MEA 003) 4) The RMP (version 2.0) is updated with regard to the clinical study reports submitted, the due dates in part III section 4, and additionally to reflect the change in SmPC based on the recent reassessment of the primary reference standard for radium-223 (issued by the National Institute of Standards and Technology (NIST)), the active moiety of Xofigo (recently approved EMEA/H/C/2653/II/011)

15.3.23. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0011

Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to include pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). As a consequence, sections 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct information regarding one of the cytochrome P450 (CYP) isoforms involved in the metabolism of riociguat in sections 4.5 and 5.2. Furthermore, the product information is brought in line with the latest QRD template (version 9.1)

15.3.24. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0042/G

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Update of section 5.1 of the SmPC following the submission of a prospective, single-arm, non-interventional, open-label cohort study conducted to investigate the safety and effectiveness in a clinical practice, study XANTUS (SN 15914) in order to fulfil MEA 025. In addition, update of section 5.1 of the SmPC following the submission of a prospective, non-interventional, open-label cohort study that was conducted in patients with acute deep vein thrombosis (DVT) to investigate the safety and effectiveness in clinical practice, study XALIA (SN 15915) in order to fulfil MEA 027. The RMP (version 9.0) is updated accordingly. Additionally the final clinical study reports for studies X-TRA (SN 16320, phase IIIb) and VENTURE-AF (SN 15694, phase IIIb) were also included in the RMP. Finally, the MAH took the opportunity to introduce a minor editorial change in the list of representatives in the package leaflets of all strengths

15.3.25. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0009

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4, 4.5 and 5.2 of the SmPC based on the completed drug-drug interaction study MK-1986-004. The Package Leaflet is updated accordingly. In addition the MAH took the opportunity to implement editorial changes in the annexes and to update the annexes in line with the latest QRD template (version 10). The RMP (version 2.0) is updated by removing the missing information for potential risks for drug-drug interactions mediated by CYP3A4, as well as addressing the identified risk for drug-drug interactions mediated via

inhibition of breast cancer resistance protein (BCRP), adding updates made to timelines for ongoing and planned studies for long term safety and Asian population experience

15.3.26. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0061

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report (CSR) for study WA29049 (single blind phase IV pharmacodynamic study to evaluate neutrophil distribution kinetics and function following single-dose tocilizumab treatment in healthy subjects) as requested in MEA 30.5. The RMP (version 19.0) is updated accordingly

15.3.27. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/X/0049/G

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Line extension to add a new pharmaceutical form (concentrate for solution for infusion), a new strength (130 mg) and a new route of administration (intravenous use) as well as an extension of indication to add as a new indication the treatment of Crohn's disease

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

Based on the assessment of the following PSURs, the 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 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 procedures including centrally authorised products only

16.1.1. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201512

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.2. Canakinumab - ILARIS (CAP) - PSUSA/00000526/201512

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201512

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.1.4. Dasabuvir - EXVIERA (CAP) - PSUSA/00010363/201512

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.5. Edoxaban - LIXIANA (CAP) - PSUSA/00010387/201512

Applicant: Daiichi Sankyo Europe GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.6. Human fibrinogen, human thrombin - EVARREST (CAP); EVICEL (CAP); RAPLIXA (CAP); TACHOSIL (CAP) - PSUSA/00010297/201512

Applicant: Omrix Biopharmaceuticals N. V. (Evicel and Evarrest), ProFibrix BV (Mallinckrodt) (Raplixa), Takeda Austria GmbH (TachoSil)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.7. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201512

Applicant: Sanofi Pasteur MSD

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.8. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201512

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.9. Lutetium (^{177}Lu) - LUMARK (CAP) - PSUSA/00010391/201512

Applicant: I.D.B. Radiopharmacy B.V.

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.10. Matrix-applied characterised autologous cultured chondrocytes - MACI (CAP) - PSUSA/00010116/201512

Applicant: Aastrom Biosciences DK ApS

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.11. Mirabegron - BETMIGA (CAP) - PSUSA/00010031/201512

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.12. Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201512

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.13. Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201512

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

16.1.14. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - PSUSA/00010367/201512

Applicant: AbbVie Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.15. Pertuzumab - PERJETA (CAP) - PSUSA/00010125/201512

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

16.1.16. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - 10 valent - SYNFLORIX (CAP) - PSUSA/00009262/201512

Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

16.1.17. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201512

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.1.18. Saquinavir - INVIRASE (CAP) - PSUSA/00002684/201512 (with RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Marianne Lunzer

Scope: Evaluation of a PSUSA procedure

16.1.19. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201512

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.1.20. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201512

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.21. Thyrotropin alfa - THYROGEN (CAP) - PSUSA/00002940/201511

Applicant: Genzyme Europe BV

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.1.22. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201512

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.23. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201512

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.24. Verteporfin - VISUDYNE (CAP) - PSUSA/00003110/201512

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.1.25. Ziconotide - PRIALT (CAP) - PSUSA/00003142/201512

Applicant: Eisai Ltd

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Doxorubicin - CAELYX (CAP); MYOCET (CAP); NAP - PSUSA/00001172/201511

Applicant: Janssen-Cilag International N.V. (Caelyx), Teva B.V. (Myocet), various

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

16.2.2. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201511

Applicant: Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.3. PSUR procedures including nationally approved products (NAPs) only

16.3.1. Alendronate, alfacalcidol (NAP) - PSUSA/00010308/201512

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.2. Atomoxetine (NAP) - PSUSA/00000262/201511

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.3. Clevidipine (NAP) - PSUSA/00010288/201511

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Dexketoprofen (NAP) - PSUSA/00000997/201510

Applicant: various

PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

16.3.5. Diacerein (NAP) - PSUSA/00001026/201512

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.6. Indapamide (NAP) - PSUSA/00001731/201511

Applicant: various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

16.3.7. Minoxidil (non-topical formulations) - PSUSA/00002066/201510

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.8. Mycophenolic acid (apart from mycophenolate mofetil) (NAP) - PSUSA/00010243/201510

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.3.9. Naltrexone (NAP) - PSUSA/00002117/201511

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

16.3.10. Rimexolone (NAP) - PSUSA/00002647/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.11. Salmeterol (NAP) - PSUSA/00002681/201510

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.12. Sultamicillin (NAP) - PSUSA/00002829/201511

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

16.3.13. Terazosin (NAP) - PSUSA/00002895/201511

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

16.3.14. Treprostinil (NAP) - PSUSA/00003013/201511

Applicant: various

PRAC Lead: Claire Ferard

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR procedures

16.4.1. Aripiprazole - ABILIFY (CAP) - EMEA/H/C/000471/LEG 075

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Leonor Chambel

Scope: Following the recommendation of PSUSA/00000234/201507, the MAH was requested to provide a review and an analysis regarding the serious adverse events under the system organ class (SOC) 'eye disorder'; a cumulative review and analysis of all events of pulmonary embolism, and review the reported cases of interaction between aripiprazole and other antipsychotics, including a discussion on this potential pharmacodynamic interaction and the possibility to submit a study to assess this interaction

16.4.2. Aripiprazole - ABILIFY MAINTENA (CAP) - EMEA/H/C/002755/LEG 007

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Following the recommendation of PSUSA/00000234/201507, submission of a review and an analysis regarding the serious adverse events under the system organ class

(SOC) 'eye disorder'; a cumulative review and analysis of all events of pulmonary embolism, and review the reported cases of interaction between aripiprazole and other antipsychotics, including a discussion on this potential pharmacodynamic interaction and the possibility to submit a study to assess this interaction

16.4.3. Colesevelam - CHOLESTAGEL (CAP) - EMEA/H/C/000512/LEG 031

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: Following the recommendation of PSUSA/00000864/201503, submission of a review on whether the ease of administration can be increased by introducing e.g. a score line or by changing the size and/or shape of the tablets, with the aim to prevent that patients split or crush tablets

16.4.4. Insulin degludec - TRESIBA (CAP) - EMEA/H/C/002498/LEG 010

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Following PSUSA/00010036/201409, submission of an updated review of all post-marketing cases (using the standard MedDRA query (SMQ) 'drug-related hepatic disorders'), including narratives

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, the 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)

17.1.1. Dinutuximab - UNITUXIN (CAP) - EMEA/H/C/PSP/0035.1

Applicant: United Therapeutics Europe Ltd

PRAC Rapporteur: Sabine Straus

Scope: Revised protocol for a PASS registry to evaluate the long-term safety outcomes of dinutuximab in high-risk neuroblastoma patients (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity and survival data)

17.1.2. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/PSP/044.1

Applicant: Celgene Europe Limited

PRAC Rapporteur: Claire Ferard

Scope: Revised protocol for a prospective non-interventional post-authorisation safety study (study CC-5013-MDS-010), designed as myelodysplastic syndromes (MDS) disease

registry of patients with transfusion dependent international prognostic scoring system (IPSS) low or intermediate-1-MDS and isolated deletion (5q)

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

17.2.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 019

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a drug utilisation study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low low-density lipoprotein (LDL)-C levels (study OBS14697)

17.2.2. Apixaban – ELIQUIS (CAP) - EMEA/H/C/002148/MEA/012.5

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: PASS protocol for study B0661073: a drug utilisation study (DUS) in Denmark to monitor potential off-label use with apixaban

17.2.3. Apremilast - OTEZLA (CAP) - EMEA/H/C/003746/MEA 006.2

Applicant: Celgene Europe Limited

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to MEA 006.1 [revised PASS protocol for CPRD (UK) data analysis for PsA and psoriasis] as per the request for supplementary information (RSI) adopted in February 2016

17.2.4. Cobicistat - TYBOST (CAP) - EMEA/H/C/002572/MEA 012.3

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 012.2 [drug utilisation study for COBI, DUS-GS-EU-216-1230: a prospective, observational drug utilisation study of cobicistat in adults with human immunodeficiency virus (HIV)-1 infection due to feasibility related issues] as per request for supplementary information (RSI) adopted by PRAC in January 2016

17.2.5. Etanercept - ENBREL (CAP) - EMEA/H/C/000262/MEA 167

Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: PASS protocol for study B1801396 investigating the relationship between etanercept exposure and major birth defects in an observational study using data from Sweden, Finland and Denmark, as per the conclusions of variation II/184

17.2.6. Ocriplasmin - JETREA (CAP) - EMEA/H/C/002381/MEA 001.1

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA001 [revised protocol for a drug utilisation study TG-MV-017 on the use of intravitreal Jetrea in clinical practice as adopted in July 2013] as per request for supplementary information (RSI) adopted by PRAC in July 2013

17.2.7. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/MEA 011.3

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: MAH's responses to MEA 011.2 [revised protocol for a PASS to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer] as per request for supplementary information (RSI) adopted by PRAC in February 2016

17.2.8. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/MEA 023.3

Applicant: Bayer Pharma AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Revised protocol for study SN 16167, a survey regarding educational materials for prescriber and patients receiving rivaroxaban for stroke prevention or deep vein thrombosis treatment post-launch

17.2.9. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.1

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 021 [revised protocol for study CLDE225A2404: a non-interventional, multi-national, multi-centre PASS to assess the long-term safety and tolerability of Odomzo (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC)] as per request for supplementary information (RSI) adopted by PRAC in February 2016

17.2.10. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/MEA 026.2

Applicant: Cardiome UK Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 026.1 [revised PASS protocol for vernakalant intravenous (IV) sterile concentrate prospective safety registry study: a prospective observational registry study to characterise normal conditions of use, dosing and safety following administration of vernakalant intravenous (IV) sterile concentrate (study 6621 049-00)] as per request for supplementary information (RSI) adopted by PRAC in March 2016

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

None

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

17.4.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS0890/0107; aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - EMEA/H/C/000964/WS0890/0077

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of the final results of study SPP100A2417: a multi-database cohort study to assess the incidence rates of colorectal hyperplasia among hypertensive patients

17.4.2. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/II/0050

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final clinical study report for study CICL670A2301 (category 3 study in the RMP), an international sentinel surveillance of patients with transfusional hemosideroris treated with Exjade in actual practice setting. This submission also served to comply with Article 46 of Regulation (EC) No 1901/2006

17.4.3. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0040

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Claire Ferard

Scope: Submission of the final clinical study report for PASS study Instanyl-5001 to evaluate the effectiveness of risk minimisation measures: a survey among health care professionals to assess their knowledge and attitudes on prescribing conditions of Instanyl in France and the Netherlands

17.4.4. Influenza vaccine (live attenuated, nasal) - FLUENZ TETRA (CAP) - EMEA/H/C/002617/II/0055

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Submission of the final clinical study report (CSR) for PASS study MA-VA-MEDI3250-1115: a post-marketing cohort study of the safety of Fluenz Tetra in subjects from 2 to 49 years of age

17.4.5. Nepafenac - NEVANAC (CAP) - EMEA/H/C/000818/II/0033

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final study report for the drug utilisation study, 'Evaluation of the use of Nepafenac in selected European populations' (category 3 study) to quantify and describe off-label use of nepafenac in order to fulfil MEA 012

17.4.6. Tacrolimus - PROTOPIC (CAP) - EMEA/H/C/000374/II/0063

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Almath Spooner

Scope: Submission of the final clinical study report of the non-interventional, registry PASS study JOELLE (JOint European Longitudinal Lymphoma and skin cancer Evaluation) final results. The RMP was updated accordingly

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

17.5.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Interim report for a long-term observational study of ataluren safety and effectiveness in usual care

Action: For adoption of advice to CHMP

17.5.2. Bazedoxifene - CONBRIZA (CAP) - EMEA/H/C/000913/MEA 012.7

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Interim report for PASS study B1781044: a cohort study of venous thromboembolism and other clinical endpoints among osteoporotic women prescribed bazedoxifene, bisphosphonates or raloxifene in Europe

17.5.3. Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - EMEA/H/C/002574/MEA 002.3

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Interim report for PASS study GS-EU-236-0141: a non-interventional PASS to assess renal risk minimisation measures among Stribild-treated patients and factors associated with the risk of proximal renal tubulopathy, and its reversibility, including event rates

17.5.4. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) - OPTAFLU (CAP) - EMEA/H/C/000758/MEA 050.3

Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's responses to MEA 050.2 [interim results of the enhanced passive safety surveillance of the seasonal cell culture trivalent influenza vaccine (Optaflu) for the 2015-16 influenza season in England in the pharmacies setting (study V58_41OB)] as per request for supplementary information (RSI) adopted by the PRAC in March 2016

17.5.5. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58[59]) - EMEA/H/W/002300/MEA 001.1

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's responses to MEA 001 [first annual report for study Malaria-076, an open extension to study Malaria-055 to evaluate long-term efficacy, safety and immunogenicity of Mosquirix against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa, describing the incidence of severe malaria in the long-term over a 3-year period (from January 2014 to December 2016) of follow-up pooled across transmission settings, in both age categories: infants 6-12 weeks and children aged 5 to 17 months] as per request for supplementary information adopted by the PRAC in March 2016

17.5.6. Tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/MEA 256.7

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Claire Ferard

Scope: MAH's responses to MEA 0256.6 [first interim results fora drug utilisation study (DUS) GS-EU-104-0433 in paediatric patients with human immunodeficiency virus (HIV-1) infection, to describe the characteristics of HIV-1 infected patients up to 18 years of age treated with Viread within the EU in order to determine if they are being managed in accordance with the European SmPC] as per request for supplementary information (RSI) as adopted by the PRAC in March 2016

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 005.7

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Fourth interim report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity

17.6.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

[59] Article 58 of Regulation (EC) No 726/2004 allows the Agency's 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)

Scope: Second interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity

17.6.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Valerie Strassmann

Scope: Third interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity

17.6.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 004.7

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Fourth interim report of the canagliflozin independent data monitoring committee (IDMC) for the DIA3008 CANVAS study as requested in the RMP additional pharmacovigilance activity

17.6.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.3

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Second interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity

17.6.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.4

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Menno van der Elst

Scope: Third interim report of the canagliflozin independent data monitoring committee (IDMC) for the NE-3001 CREDENCE study as requested in the RMP additional pharmacovigilance activity

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the 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 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. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0064 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Rafe Suvarna

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/R/0004 (without RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Jana Mladá

Scope: Conditional renewal of the marketing authorisation

18.2.2. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0035 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Alendronic acid, colecalciferol - ADROVANCE (CAP) - EMEA/H/C/000759/R/0036 (without RMP)

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.2. Azilsartan medoxomil - EDARBI (CAP) - EMEA/H/C/002293/R/0018 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.3. Colistimethate sodium - COLOBREATHE (CAP) - EMEA/H/C/001225/R/0024 (without RMP)

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

18.3.4. Desloratadine - DESLORATADINE ACTAVIS (CAP) - EMEA/H/C/002435/R/0008 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Jean-Michel Dogné

Scope: 5-year renewal of the marketing authorisation

18.3.5. Efavirenz - EFAVIRENZ TEVA (CAP) - EMEA/H/C/002352/R/0018 (without RMP)

Applicant: Teva B.V.

PRAC Rapporteur: Margarida Guimarães

Scope: 5-year renewal of the marketing authorisation

18.3.6. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/R/0065 (without RMP)

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Rafe Suvarna

Scope: 5-year renewal of the marketing authorisation

18.3.7. Levetiracetam - LEVETIRACETAM ACTAVIS (CAP) - EMEA/H/C/002355/R/0013 (without RMP)

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

18.3.8. Levetiracetam - LEVETIRACETAM SUN (CAP) - EMEA/H/C/002051/R/0013 (without RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Veerle Verlinden

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pioglitazone, glimepiride - TANDEMACT (CAP) - EMEA/H/C/000680/R/0049 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.10. Piperaquine tetraphosphate, artenimol - EURARTESIM (CAP) - EMEA/H/C/001199/R/0023 (without RMP)

Applicant: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.11. Repaglinide - REPAGLINIDE ACCORD (CAP) - EMEA/H/C/002318/R/0005 (without RMP)

Applicant: Accord Healthcare Ltd

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.12. Sunitinib - SUTENT (CAP) - EMEA/H/C/000687/R/0062 (with RMP)

Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope: 5-year renewal of the marketing authorisation

18.3.13. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/R/0034 (without RMP)

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

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 4-8 July 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Yuliyan Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Claire Ferard	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Leonidas Klironomos	Member	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	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
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No restrictions applicable to this meeting	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No interests declared	Full involvement
Brigitte	Member	Independent	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Keller-Stanislawski		scientific expert	declared	
Thierry Trenque	Member	Independent scientific expert	No interests declared	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member - via telephone*	Patients' Organisation Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Martin Erik Nyeland	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Pierre Demolis	Expert - in person*	France	No interests declared	Full involvement
Caroline Laborde	Expert - in person*	France	No interests declared	Full involvement
Nathalie Morgensztejn	Expert - in person*	France	No interests declared	Full involvement
Tania Meier	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Eleanor Carey	Expert - via telephone*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - via telephone*	Ireland	No restrictions applicable to this meeting	Full involvement
Gunta Pauksena	Expert - in person*	Latvia	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
Negar Babae	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Florianne Bauer	Expert - in person*	Netherlands	No interests declared	Full involvement
Désirée Bergamin	Expert - in person*	Netherlands	No interests declared	Full involvement
Reynold Francisca	Expert - in person*	Netherlands	No interests declared	Full involvement
Pieter de Graeff	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Helga Haugom Olsen	Expert - in person*	Norway	No interests declared	Full involvement
Justyna Paterak	Expert - via telephone*	Poland	No interests declared	Full involvement
Joanna Plichta	Expert - in person*	Poland	No interests declared	Full involvement
Nuno Janeiro	Expert - via telephone*	Portugal	No restrictions applicable to this meeting	Full involvement
Magda Pedro	Expert - via telephone*	Portugal	No interests declared	Full involvement
Natividad Galiana LLorca	Expert - via telephone*	Spain	No restrictions applicable to this meeting	Full involvement
Miguel Angel Maciá	Expert - via telephone*	Spain	No interests declared	Full involvement
Consuelo Mejías Pavón	Expert - in person*	Spain	No interests declared	Full involvement
Maria del Pilar Rayón	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - in person*	Sweden	No interests declared	Full involvement
Karl Mikael Kälkner	Expert - via telephone*	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
Jan Sjöberg	Expert - in person*	Sweden	No interests declared	Full involvement
Inga Bellahn	Expert - in person*	United Kingdom	No interests declared	Full involvement
Mattia Calissano	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Katherine Donegan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jennifer Matthissen	Expert - in person*	United Kingdom	No interests declared	Full involvement
Anna Radecka	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Andrew Ruddick	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only 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: www.ema.europa.eu/