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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of meeting on 09 – 12 March 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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Table of contents

1.	Introduction	14
1.1.	Welcome and declarations of interest of members, alternates and experts	14
1.2.	Agenda of the meeting on 09 - 12 March 2020	14
1.3.	Minutes of the previous meeting on 10 - 13 February 2020.....	14
2.	EU referral procedures for safety reasons: urgent EU procedures	15
2.1.	Newly triggered procedures	15
2.2.	Ongoing procedures	15
2.3.	Procedures for finalisation.....	15
2.4.	Planned public hearings.....	15
3.	EU referral procedures for safety reasons: other EU referral procedures	15
3.1.	Newly triggered procedures	15
3.1.1.	Ifosfamide (NAP) - EMEA/H/A-31/1495	15
3.1.2.	Ulipristal acetate – ESMYA (CAP); NAP - EMEA/H/A-31/1496.....	16
3.2.	Ongoing procedures	18
3.2.1.	Leuprorelin (NAP) - EMEA/H/A-31/1486.....	18
3.3.	Procedures for finalisation.....	19
3.3.1.	Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP flucytosine (NAP); 5-fluorouracil (5-FU) (NAP); tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP) - EMEA/H/A-31/1481	19
3.4.	Re-examination procedures.....	21
3.5.	Others	21
4.	Signals assessment and prioritisation	21
4.1.	New signals detected from EU spontaneous reporting systems	21
4.2.	New signals detected from other sources	21
4.2.1.	Amitriptyline (NAP); bupropion (NAP); citalopram (NAP); desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP), XERISTAR (CAP), NAP; escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); milnacipran (NAP); mirtazapine (NAP); naltrexone, bupropion – MYSIMBA (CAP); paroxetine (NAP); sertraline (NAP); trazodone (NAP); venlafaxine (NAP); vortioxetine – BRINTELLIX (CAP)	21
4.2.2.	Lopinavir, ritonavir – ALUVIA (Art 58), KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP); NAP	23
4.2.3.	Interferon alfa-2a (NAP); interferon alfa-2b - INTRONA (CAP); peginterferon alfa-2a – PEGASYS (CAP); peginterferon alfa-2b - PEGINTRON (CAP), VIRAFERONPEG (CAP)	24
4.3.	Signals follow-up and prioritisation.....	25
4.3.1.	Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP; Selective serotonin reuptake inhibitors (SSRIs):	

	citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP); imipramine (NAP); nortriptyline (NAP); trimipramine (NAP); Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP); phenelzine (NAP); selegiline (NAP); tranylcypromine (NAP); Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); lithium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP); Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan(NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP); Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP); tropisetron (NAP); Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP).....	25
4.3.2.	Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP); dienestrol (NAP); diethylstilbestrol (NAP); estradiol (NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); methallenestril (NAP); moxestrol (NAP); promestriene (NAP); tibolone (NAP).....	26
4.3.3.	Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/018.1; avelumab – BAVENCIO (CAP) - EMEA/H/C/004338/SDA/005; cemiplimab – LIBTAYO (CAP) EMEA/H/C/004844/SDA/004.1; durvalumab – IMFINZI (CAP) EMEA/H/C/004771/SDA/003.1; ipilimumab – YERVOY (CAP) EMEA/H/C/002213/SDA/039; nivolumab – OPDIVO (CAP) EMEA/H/C/003985/SDA/039; pembrolizumab - KEYTRUDA (CAP) EMEA/H/C/003820/SDA/024	27
4.3.4.	Mycophenolic acid (NAP); mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/SDA/040, MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP), NAP	28
4.3.5.	Paroxetine (NAP)	28
4.3.6.	Thiazide, thiazide-like diuretics and combinations: bendroflumethiazide (NAP); chlortalidone (NAP); cicletanine (NAP); clopamide (NAP); cyclopenthiiazide (NAP); hydrochlorothiazide (NAP); hydrochlorothiazide, aliskiren – RASILEZ HCT (CAP); hydrochlorothiazide, amlodipine, valsartan - EXFORGE HCT (CAP); hydrochlorothiazide, irbesartan – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); hydrochlorothiazide, telmisartan – ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP); hydrochlorothiazide, valsartan, amlodipine - COPALIA HCT (CAP), DAFIRO HCT (CAP); hydroflumethiazide (NAP); indapamide (NAP); metipamide (NAP); metolazone (NAP); xipamide (NAP)	29

5. Risk management plans (RMPs) 30

5.1.	Medicines in the pre-authorisation phase	30
5.1.1.	Aripiprazole - EMEA/H/C/005062	30
5.1.2.	Autologous CD34 ⁺ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene - EMEA/H/C/005321, Orphan.....	30
5.1.3.	Fenfluramine - EMEA/H/C/003933, Orphan	30
5.1.4.	Lefamulin - EMEA/H/C/005048	30
5.1.5.	Obiltoxaximab - EMEA/H/C/005169, Orphan	30

5.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	31
5.2.1.	Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/WS1713/0109; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/WS1713/0083; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS1713/0075; lamivudine, abacavir, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/WS1713/0115	31
5.2.2.	Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0052	32
5.2.3.	Human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) - EMEA/H/C/002493/II/0042	33
5.2.4.	Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0052	34
5.3.	Medicines in the post-authorisation phase – CHMP-led procedures	34
6.	Periodic safety update reports (PSURs)	35
6.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	35
6.1.1.	Cobicistat - TYBOST (CAP) - PSUSA/00010081/201908	35
6.1.2.	Dronedarone - MULTAQ (CAP) - PSUSA/00001180/201907	35
6.1.3.	Linacotide - CONSTELLA (CAP) - PSUSA/00010025/201908	36
6.1.4.	Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201908.....	37
6.1.5.	Patisiran - ONPATTRO (CAP) - PSUSA/00010715/201908	38
6.1.6.	Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201909	38
6.1.7.	Romiplostim - NPLATE (CAP) - PSUSA/00002660/201907	39
6.1.8.	Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201908.....	40
6.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)	41
6.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	41
6.3.1.	Brivudine (NAP) - PSUSA/00000434/201907	41
6.3.2.	Busulfan (NAP) - PSUSA/00000464/201907	42
6.3.3.	Ropinirole (NAP) - PSUSA/00002661/201907	43
6.4.	Follow-up to PSUR/PSUSA procedures	43
7.	Post-authorisation safety studies (PASS)	43
7.1.	Protocols of PASS imposed in the marketing authorisation(s).....	43
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	43
7.2.1.	Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002.1	44
7.3.	Results of PASS imposed in the marketing authorisation(s)	44
7.3.1.	Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0024	44
7.4.	Results of PASS non-imposed in the marketing authorisation(s).....	45
7.4.1.	Linacotide - CONSTELLA (CAP) - EMEA/H/C/002490/II/0043	45
7.4.2.	Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0030, Orphan.....	46
7.4.3.	Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0043.....	47

7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	48
7.5.1.	Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/ANX 006.1	48
7.5.2.	Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/ANX 005.1.....	49
7.5.3.	Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/ANX 001.....	49
7.5.4.	Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/ANX 016.1	50
7.5.5.	Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/ANX 006.1	51
7.5.6.	Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/ANX 023.1.....	51
7.5.7.	Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/ANX 009.1	52
7.5.8.	Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/ANX 004.....	53
7.6.	Others	53
7.6.1.	Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/REC 002.....	53
7.7.	New Scientific Advice	54
7.8.	Ongoing Scientific Advice	54
7.9.	Final Scientific Advice (Reports and Scientific Advice letters)	54
8.	Renewals of the marketing authorisation, conditional renewal and annual reassessments	54
8.1.	Annual reassessments of the marketing authorisation	54
8.2.	Conditional renewals of the marketing authorisation	54
8.3.	Renewals of the marketing authorisation	54
9.	Product related pharmacovigilance inspections	55
9.1.	List of planned pharmacovigilance inspections.....	55
9.2.	Ongoing or concluded pharmacovigilance inspections.....	55
9.3.	Others	55
10.	Other safety issues for discussion requested by the CHMP or the EMA	55
10.1.	Safety related variations of the marketing authorisation.....	55
10.1.1.	Olanzapine - OLANZAPINE APOTEX (CAP) - EMEA/H/C/001178/II/0037.....	55
10.2.	Timing and message content in relation to Member States' safety announcements	56
10.3.	Other requests.....	56
10.4.	Scientific Advice	56
11.	Other safety issues for discussion requested by the Member States	56
11.1.	Safety related variations of the marketing authorisation.....	56
11.1.1.	Fentanyl (NAP) - NL/H/3915/II/007/G.....	56
11.1.2.	Paracetamol (NAP) - IE/H/0835/001/II/056/G, PA0678/037/001	57
11.2.	Other requests.....	57
11.2.1.	Bupropion (NAP) - NL/H/PSUFU/00000461/201812.....	57

12.	Organisational, regulatory and methodological matters	58
12.1.	Mandate and organisation of the PRAC	58
12.2.	Coordination with EMA Scientific Committees or CMDh-v	58
12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	58
12.4.	Cooperation within the EU regulatory network	58
12.4.1.	EudraVigilance data analysis system (EVDAS) - training for National Competent Authorities (NCAs)	58
12.4.2.	PRAC strategic review and learning meeting (SRLM) under the Croatian presidency of the European Union (EU) Council - Split, Croatia, 22-24 April 2020 - Agenda	58
12.5.	Cooperation with International Regulators	58
12.6.	Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee	59
12.7.	PRAC work plan	59
12.8.	Planning and reporting	59
12.9.	Pharmacovigilance audits and inspections	59
12.9.1.	Pharmacovigilance systems and their quality systems	59
12.9.2.	Pharmacovigilance inspections	59
12.9.3.	Pharmacovigilance audits	59
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list	59
12.10.1.	Periodic safety update reports	59
12.10.2.	Granularity and Periodicity Advisory Group (GPAG)	59
12.10.3.	PSURs repository	59
12.10.4.	Union reference date list – consultation on the draft list	59
12.11.	Signal management	60
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group	60
12.12.	Adverse drug reactions reporting and additional monitoring	60
12.12.1.	Additional monitoring – status of lenalidomide-containing product(s)	60
12.12.2.	List of products under additional monitoring – consultation on the draft list	60
12.12.3.	Management and reporting of adverse reactions to medicinal products	60
12.13.	EudraVigilance database	60
12.13.1.	Activities related to the confirmation of full functionality	60
12.13.2.	EudraVigilance – annual report 2019	60
12.14.	Risk management plans and effectiveness of risk minimisations	61
12.14.1.	Risk management systems	61
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations	61
12.14.3.	Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – request for input on terminology	61
12.15.	Post-authorisation safety studies (PASS)	61

12.15.1.	EU post-authorisation safety studies (EU PAS) register - notification of imposed studies registered in the EU PASS Register to Member States	61
12.15.2.	Post-authorisation Safety Studies – imposed PASS	61
12.15.3.	Post-authorisation Safety Studies – non-imposed PASS	61
12.16.	Community procedures.....	62
12.16.1.	Referral procedures for safety reasons	62
12.17.	Renewals, conditional renewals, annual reassessments	62
12.18.	Risk communication and transparency	62
12.18.1.	Public participation in pharmacovigilance	62
12.18.2.	Safety communication	62
12.19.	Continuous pharmacovigilance	62
12.19.1.	Incident management	62
12.20.	Others	62
12.20.1.	Drug-induced hepatotoxicity – draft PRAC guidance	62
12.20.2.	EMA new organisational structure for human medicines division	62
12.20.3.	Medical Dictionary for Regulatory Activities (MedDRA) points to consider group – call for EU expert nomination	62
12.20.4.	Serious cutaneous adverse reactions (SCARs) - PRAC guidance update	63
13.	Any other business	63
14.	Annex I – Signals assessment and prioritisation	63
14.1.	New signals detected from EU spontaneous reporting systems	63
14.1.1.	Apixaban – ELIQUIS (CAP).....	63
14.1.2.	Dabigatran – PRADAXA (CAP)	63
14.1.3.	Lamotrigine (NAP)	64
14.2.	New signals detected from other sources	64
15.	Annex I – Risk management plans	64
15.1.	Medicines in the pre-authorisation phase	64
15.1.1.	Apixaban - EMEA/H/C/005358.....	64
15.1.2.	Doxorubicin - EMEA/H/C/005320	64
15.1.3.	Indacaterol, mometasone furoate - EMEA/H/C/005516.....	64
15.1.4.	Melphalan - EMEA/H/C/005173	64
15.1.5.	Methylthionium chloride - EMEA/H/C/002776.....	65
15.1.6.	Trastuzumab - EMEA/H/C/005209	65
15.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	65
15.2.1.	5-aminolevulinic acid - AMELUZ (CAP) - EMEA/H/C/002204/II/0040	65
15.2.2.	Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0033, Orphan.....	65
15.2.3.	Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/II/0015, Orphan	65
15.2.4.	Follitropin alfa - GONAL-F (CAP) - EMEA/H/C/000071/II/0147	66

15.2.5.	Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/II/0066	66
15.2.6.	Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/II/0081	66
15.2.7.	Lonococog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/II/0030	66
15.2.8.	Lopinavir, ritonavir - ALUVIA (Art 58) - EMEA/H/W/000764/WS1711/0112;KALETRA (CAP) - EMEA/H/C/000368/WS1711/0181.....	67
15.2.9.	Ponatinib - ICLUSIG (CAP) - EMEA/H/C/002695/II/0053, Orphan	67
15.2.10.	Telotristat ethyl - XERMELO (CAP) - EMEA/H/C/003937/II/0021, Orphan.....	67
15.3.	Medicines in the post-authorisation phase – CHMP-led procedures	67
15.3.1.	Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0070	68
15.3.2.	Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0033.....	68
15.3.3.	Autologous CD34 ⁺ enriched cell fraction that contains CD34 ⁺ cells transduced with retroviral vector that encodes for the human ANA cDNA sequence - STRIMVELIS (CAP) - EMEA/H/C/003854/II/0024, Orphan.....	68
15.3.4.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0016.....	68
15.3.5.	Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0008/G.....	69
15.3.6.	Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/II/0001/G	69
15.3.7.	Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/X/0007/G, Orphan	69
15.3.8.	Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0015.....	70
15.3.9.	Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/II/0053/G	70
15.3.10.	Desloratadine - DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/II/0023/G.....	71
15.3.11.	Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/X/0045	71
15.3.12.	Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/II/0058	71
15.3.13.	Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0020	72
15.3.14.	Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0106	72
15.3.15.	Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0018/G.....	72
15.3.16.	Iron - VELPHORO (CAP) - EMEA/H/C/002705/II/0021	72
15.3.17.	Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0083/G, Orphan.....	73
15.3.18.	Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0019/G, Orphan	73
15.3.19.	Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0030	73
15.3.20.	Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/X/0007.....	73
15.3.21.	Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/II/0030.....	74
15.3.22.	Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0029	74
15.3.23.	Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0023	74
15.3.24.	Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0088	75
15.3.25.	Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0027, Orphan.....	75
15.3.26.	Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/II/0050	75
15.3.27.	Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0035	75

15.3.28.	Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0036	76
15.3.29.	Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/II/0146	76
15.3.30.	Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0038.....	76
15.3.31.	Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0002.....	76
15.3.32.	Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1724/0029; RITEMVIA (CAP) - EMEA/H/C/004725/WS1724/0029; TRUXIMA (CAP) - EMEA/H/C/004112/WS1724/0032... 77	
15.3.33.	Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0044.....	77
15.3.34.	Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/II/0026/G, Orphan.....	77
15.3.35.	Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0053/G	78
15.3.36.	Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0024.....	78
15.3.37.	Talazoparib - TALZENNA (CAP) - EMEA/H/C/004674/II/0001.....	78
15.3.38.	Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/X/0015/G, Orphan.....	79
15.3.39.	Thiotepa - TEPADINA (CAP) - EMEA/H/C/001046/X/0036, Orphan	79
15.3.40.	Trastuzumab - OGIVRI (CAP) - EMEA/H/C/004916/II/0009.....	79

16. Annex I - Periodic safety update reports (PSURs) 79

16.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	80
16.1.1.	Agalsidase beta - FABRAZYME (CAP) - PSUSA/00000070/201907	80
16.1.2.	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (Δ LNGBFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS - PSUSA/00010530/201908	80
16.1.3.	Asenapine - SYCREST (CAP) - PSUSA/00000256/201908.....	80
16.1.4.	Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201908	80
16.1.5.	Burosumab - CRYSVITA (CAP) - PSUSA/00010669/201908.....	80
16.1.6.	Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/201908	80
16.1.7.	Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201908.....	81
16.1.8.	Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201908	81
16.1.9.	Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201908	81
16.1.10.	Copper (^{64}Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201908.....	81
16.1.11.	Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/201908.....	81
16.1.12.	Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/201908	81
16.1.13.	Doravirine - PIFELTRO (CAP) - PSUSA/00010729/201908.....	81
16.1.14.	Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - PSUSA/00010731/201908	82
16.1.15.	Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201908	82
16.1.16.	Eravacycline - XERAVA (CAP) - PSUSA/00010718/201908	82
16.1.17.	Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201908.....	82
16.1.18.	Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201908	82

16.1.19.	Human alpha ₁ -proteinase inhibitor - RESPREEZA (CAP) - PSUSA/00010410/201908	82
16.1.20.	Hydrocortisone - ALKINDI (CAP) - PSUSA/00010674/201908	83
16.1.21.	Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201908	83
16.1.22.	Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/201908	83
16.1.23.	Mecasermin - INCRELEX (CAP) - PSUSA/00001942/201908	83
16.1.24.	Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/201908	83
16.1.25.	Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201908.....	83
16.1.26.	Pandemic influenza vaccine (H5N1) (whole virion, Vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); prepandemic influenza vaccine (H5N1) (whole virion, Vero cell derived, inactivated) - VEPACEL (CAP) - PSUSA/00002282/201908	83
16.1.27.	Peginterferon alfa-2b - PEGINTRON (CAP); VIRAFERONPEG (CAP) - PSUSA/00002327/201907	84
16.1.28.	Pyronaridine, artesunate - PYRAMAX (Art 58) - EMEA/H/W/002319/PSUV/0021	84
16.1.29.	Rolapitant - VARUBY (CAP) - PSUSA/00010592/201908	84
16.1.30.	Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/201908.....	84
16.1.31.	Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201908.....	84
16.1.32.	Telotristat - XERMELO (CAP) - PSUSA/00010639/201908	84
16.1.33.	Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/201908	85
16.1.34.	Tisagenlecleucel - KYMRIAHA (CAP) - PSUSA/00010702/201908	85
16.1.35.	Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201908	85
16.1.36.	Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201908	85
16.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	85
16.2.1.	Palonosetron - ALOXI (CAP); NAP - PSUSA/00002268/201907	85
16.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	85
16.3.1.	Beclometasone, formoterol (NAP) - PSUSA/00010068/201907	85
16.3.2.	Fosfomycin (NAP) - PSUSA/00010336/201907	86
16.3.3.	Fosfomycin (NAP) - PSUSA/00010326/201907	86
16.3.4.	Human coagulation factor IX (NAP) - PSUSA/00001617/201907.....	86
16.3.5.	Meloxicam (NAP) - PSUSA/00010474/201907	86
16.3.6.	Phleum pratense (NAP) - PSUSA/00010475/201907	86
16.3.7.	Poliovirus type 1, poliovirus type 3 (oral, live, attenuated) vaccine (NAP) - PSUSA/00010642/201907	86
16.3.8.	Zaleplon (NAP) - PSUSA/00003140/201907	86
16.4.	Follow-up to PSUR/PSUSA procedures	87
17.	Annex I – Post-authorisation safety studies (PASS)	87
17.1.	Protocols of PASS imposed in the marketing authorisation(s).....	87

17.1.1.	Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSA/S/0049	87
17.1.2.	Cholic acid - KOLBAM (CAP) - EMEA/H/C/PSA/S/0048	87
17.1.3.	Valproate (NAP) - EMEA/H/N/PSP/J/0074.2.....	87
17.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	88
17.2.1.	Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.9	88
17.2.2.	Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002	88
17.2.3.	Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 002.1.....	88
17.2.4.	Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 003.1.....	88
17.2.5.	Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 005	88
17.2.6.	Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 009	89
17.2.7.	Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 020	89
17.2.8.	Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020.....	89
17.2.9.	Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.2	89
17.2.10.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003	89
17.2.11.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 004	90
17.2.12.	Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005	90
17.2.13.	Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.6	90
17.2.14.	Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.1	90
17.2.15.	Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.1	90
17.3.	Results of PASS imposed in the marketing authorisation(s).....	91
17.4.	Results of PASS non-imposed in the marketing authorisation(s).....	91
17.4.1.	Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/II/0113.....	91
17.4.2.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0079.....	91
17.4.3.	Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0073.....	91
17.4.4.	Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0063/G	92
17.4.5.	Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1742/0037; FORXIGA (CAP) - EMEA/H/C/002322/WS1742/0056; dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1742/0043; XIGDUO (CAP) - EMEA/H/C/002672/WS1742/0054	92
17.4.6.	Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0048.....	92
17.4.7.	Maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/II/0061	93
17.4.8.	Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0094	93
17.4.9.	Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/WS1761/0028; ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/WS1761/0013 Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1761/0029; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1761/0032.....	93
17.4.10.	Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0074/G	93
17.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	94

17.5.1.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.12.....	94
17.5.2.	Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.12.....	94
17.5.3.	Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.5.....	94
17.5.4.	Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.11.....	94
17.5.5.	Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062.....	95
17.5.6.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005.2.....	95
17.5.7.	Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005.2.....	95
17.5.8.	Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002.2.....	95
17.5.9.	Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 024.....	96
17.5.10.	Florbetaben (¹⁸ F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.9.....	96
17.5.11.	Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/LEG 188.6.....	96
17.5.12.	Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.8.....	96
17.5.13.	Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 005.2.....	96
17.5.14.	Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/MEA 008.4.....	97
17.5.15.	Lutetium (¹⁷⁷ Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.3.....	97
17.5.16.	Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/LEG 006.....	97
17.5.17.	Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.2.....	97
17.5.18.	Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.2.....	98
17.5.19.	Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/ANX 002.1.....	98
17.5.20.	Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.6.....	98
17.6.	Others	98
17.6.1.	Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/MEA 062.....	98
17.6.2.	Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060.2.....	98
17.7.	New Scientific Advice	99
17.8.	Ongoing Scientific Advice	99
17.9.	Final Scientific Advice (Reports and Scientific Advice letters)	99
18.	Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments	99
18.1.	Annual reassessments of the marketing authorisation	99
18.1.1.	Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0031 (with RMP).....	99
18.1.2.	Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0036 (without RMP).....	99
18.1.3.	Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0009 (with RMP).....	100
18.1.4.	Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0055 (without RMP).....	100
18.2.	Conditional renewals of the marketing authorisation	100
18.2.1.	Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0006 (without RMP).....	100
18.3.	Renewals of the marketing authorisation	100
18.3.1.	Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/R/0055 (without RMP).....	100
18.3.2.	Aripiprazole - ARIPIPRAZOLE SANDOZ (CAP) - EMEA/H/C/004008/R/0014 (without RMP).....	100

18.3.3.	Aripiprazole - ARIPIPRAZOLE ZENTIVA (CAP) - EMEA/H/C/003899/R/0012 (with RMP)	100
18.3.4.	Duloxetine - DULOXETINE ZENTIVA (CAP) - EMEA/H/C/003935/R/0009 (with RMP)	100
18.3.5.	Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/R/0022 (without RMP)	101
18.3.6.	Idebenone - RAXONE (CAP) - EMEA/H/C/003834/R/0020 (without RMP)	101
18.3.7.	Isavuconazole - CRESEMBA (CAP) - EMEA/H/C/002734/R/0027 (without RMP)	101
18.3.8.	Ivabradine - IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/R/0014 (with RMP)	101
18.3.9.	Pemetrexed - PEMETREXED LILLY (CAP) - EMEA/H/C/004114/R/0011 (with RMP)	101
18.3.10.	Pregabalin - PREGABALIN ACCORD (CAP) - EMEA/H/C/004024/R/0015 (with RMP)	101
18.3.11.	Pregabalin - PREGABALIN SANDOZ (CAP) - EMEA/H/C/004010/R/0012 (with RMP)	101
18.3.12.	Pregabalin - PREGABALIN SANDOZ GMBH (CAP) - EMEA/H/C/004070/R/0013 (with RMP)	102
18.3.13.	Pregabalin - PREGABALIN ZENTIVA (CAP) - EMEA/H/C/003900/R/0021 (with RMP)	102
18.3.14.	Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/R/0039 (without RMP)	102
18.3.15.	Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/R/0028 (without RMP)	102
18.3.16.	Sufentanil - ZALVISO (CAP) - EMEA/H/C/002784/R/0016 (without RMP)	102
18.3.17.	Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/R/0045 (without RMP)	102
18.3.18.	Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/R/0037 (without RMP)	102

19.	Annex II – List of participants	103
20.	Annex III - List of acronyms and abbreviations	111
21.	Explanatory notes	111

1. Introduction

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

The Chairperson opened the 09 – 12 March 2020 meeting. In light of the current crisis (COVID-19 outbreak), the EMA invoked the Business Continuity Plan (BCP) and exceptional measures taken to protect the staff members and all delegates, experts and members of the Committee. This entails that the participation and the voting from remote are allowed as a temporary measure, based on the current exceptional circumstances. The Chairperson asked for confirmation of the number of participants and of the quorum, and once received assurance by the PRAC secretariat, requested participants to state if they had any objection to hold the meeting and to take decisions (by consensus or by voting) in such a way. No objection was raised. In light of the unanimous agreement of all members to hold the meeting in a virtual mode, the Chair confirmed the validity of the notice of the meeting and proceeded to welcome the new members and alternates.

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). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

1.2. Agenda of the meeting on 09 - 12 March 2020

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 10 - 13 February 2020

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 10 - 13 February 2020 were published on the EMA website on 28 July 2020 ([EMA/PRAC/404462/2020](https://www.ema.europa.eu/en/PRAC/404462/2020)).

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. Ifosfamide¹ (NAP) - EMEA/H/A-31/1495

Applicant(s): various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Željana Margan Koletić

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

Background

Ifosfamide is an alkylating agent indicated in the treatment of various malignancies in oncology and haematology for children and adults.

The French Medicines Agency² ([ANSM](#)) sent a letter of [notification](#) dated 28 February 2020 of a referral under Article 31 of Directive 2001/83/EC for the review of the risk of encephalopathy associated to ifosfamide-containing solutions. A signal was under review at the PRAC following the observation by France of an increased incidence of encephalopathy with ifosfamide-containing solutions compared to the powder for solution. The signal was initiated after a national pharmacovigilance survey in France reporting clusters of cases of encephalopathy associated with ifosfamide. In addition, two epidemiological studies, namely a national pharmacovigilance case-control follow-up study³ in the paediatric population and a

¹ Solution, concentrate for solution

² Agence Nationale de Sécurité du Médicament et des Produits de Santé

³ Hillaire-Buys D, Mousset M, Allouchery M et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a pediatric population. *Thérapie*. 2019 Oct 28

retrospective study⁴ using data from medical records of adult patients, observed a higher rate of encephalopathy in patients treated with ifosfamide EG (ifosfamide) solution compared to ifosfamide powder for solution. In February 2020, the PRAC concurred that the evaluated epidemiological studies suggest an increased risk for ifosfamide-induced encephalopathy with ifosfamide EG (ifosfamide) solution for infusion compared with ifosfamide powder. While it is acknowledged that uncertainties remain, the PRAC agreed that the data raise serious concerns that need to be further addressed. For further background, see [PRAC minutes December 2019](#)⁵ and [PRAC minutes February 2020](#).

Therefore, the ANSM considered in the interest of the Union to refer the matter to the PRAC for further evaluation and requested that it gives its recommendation as to whether the marketing authorisation(s) for ifosfamide-containing solutions should be maintained, varied, suspended or revoked.

Discussion

The PRAC noted the notification letter from the ANSM.

The Committee appointed Martin Huber as Rapporteur and Željana Margan Koletić as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs for ifosfamide-containing solution(s) ([EMA/PRAC/111337/2020](#)) and a timetable for the procedure ([EMA/PRAC/111338/2020](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure⁶ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release ([EMA/116503/2020](#)) entitled 'EMA starts review of certain ifosfamide cancer medicines'.

3.1.2. Ulipristal acetate⁷ – ESMYA (CAP); NAP - EMEA/H/A-31/1496

Applicant(s): Gedeon Richter Plc.; various

PRAC Rapporteur: Annika Folin; PRAC Co-rapporteur: Menno van der Elst

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

⁴ Chambord J, Henny F, Salleron J et al. Ifosfamide-induced encephalopathy: Brand-name (Holoxan) vs generic formulation (Ifosfamide EG). *J Clin Pharm Ther.* 2019;44:372-380

⁵ Held 25-28 November 2019

⁶ Rules of procedure on the organisation and conduct of public hearings at the PRAC

⁷ 5 mg

Background

Ulipristal acetate is an orally active synthetic selective progesterone receptor modulator (SPRM). The 5 mg form is indicated, as Esmya a centrally authorised medicine and nationally-approved medicines, for a single treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

The European Commission (EC) sent a letter of [notification](#) dated 5 March 2020 triggering a procedure under a referral under Article 31 of Directive 2001/83/EC for the review of ulipristal acetate 5 mg-containing products.

In May 2018, the PRAC finalised a review of the benefit-risk balance of Esmya (ulipristal acetate) under Article 20 of Regulation (EC) No 726/2004 initiated due to cases of serious liver injury leading to liver transplantation. The review outcome includes a restriction of the indications, a contraindication in patients with underlying hepatic disorder, liver tests before, during and after the first two treatment courses, and a discontinuation of treatment in case of elevated transaminases or symptoms compatible with liver injury. For further background, see [PRAC minutes May 2018](#).

In December 2019, a new case of serious liver injury leading to liver transplantation following exposure to Esmya (ulipristal acetate) was reported. Despite adherence to the implemented risk minimisation measures (RMMs), the progression in the development of hepatic failure leading to liver transplantation could not be prevented. Therefore, the EC requested the EMA to give its opinion by 30 September 2020 as to whether the marketing authorisations for ulipristal acetate 5 mg-containing products should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal products.

Discussion

The PRAC noted the notification letter from the EC.

The PRAC appointed Annika Folin as Rapporteur and Menno van der Elst as Co-Rapporteur for the procedure.

The PRAC reviewed the information currently available to the Committee on ulipristal acetate 5 mg as well as data provided by the MAH of Esmya (ulipristal acetate) in writing and in an oral explanation on the fifth case of liver injury requiring liver transplantation reported with ulipristal acetate 5 mg. The PRAC reviewed the new case and concluded on a probable causal association with the use of ulipristal acetate 5 mg. The PRAC also noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented despite the RMMs previously implemented were followed.

Taking into account the seriousness of the reported adverse event, the fact that this case occurred despite adherence to the RMMs in place, and that the approved indication(s) concern(s) symptomatic treatment, the PRAC concluded that this new case has an impact on the benefit-risk balance of ulipristal acetate 5 mg and that temporary measures are needed to protect public health during the review.

Based on the currently available information, the PRAC could not identify at this stage measures that would sufficiently mitigate the risk of serious liver disorders in all patients

treated with ulipristal acetate 5 mg. Therefore, the PRAC recommended that the marketing authorisations of ulipristal acetate 5 mg are suspended while a thorough assessment of all available data related to the benefit-risk of ulipristal acetate 5 mg and effectiveness of the RMMs is performed.

Finally, the PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

Summary of recommendation(s)/conclusions

- The PRAC recommended as a provisional measure the suspension of marketing authorisations of ulipristal acetate 5 mg-containing products, without prejudice to the final conclusions of the ongoing procedure under Article 31 of Directive 2001/83/EC.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.
- The Committee adopted a LoQ to the MAHs for ulipristal acetate 5 mg-containing products ([EMA/PRAC/121855/2020](#)) and a timetable for the procedure ([EMA/PRAC/121857/2020](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure⁸ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure, as needed.

See EMA press release ([EMA/121879/2020](#)) entitled 'Suspension of ulipristal acetate for uterine fibroids during ongoing EMA review of liver injury risk'.

Post-meeting note: On 25 March 2020, the European Commission (EC) issued a Commission Decision (CD) on the provisional measures ([C\(2020\) 1977 final](#)). On 2 April 2020, the PRAC assessment report on provisional measures ([EMA/70192/2018](#)) was published on the EMA website.

3.2. Ongoing procedures

3.2.1. Leuprorelin⁹ (NAP) - EMEA/H/A-31/1486

Applicant(s): various

PRAC Rapporteur: Željana Margan Koletić; PRAC Co-rapporteur: Eva Segovia

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

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of leuprorelin-containing products after reports indicated that handling errors with the products

⁸ Rules of procedure on the organisation and conduct of public hearings at the PRAC

⁹ Depot formulation(s)

during preparation and administration can cause some patients to receive insufficient amounts of their medicine, potentially leading to a lack of efficacy. As the significant number of medication errors observed for leuprorelin-containing depot products remain a serious risk to public health, it was considered that further action is warranted to further characterise and mitigate the risk of handling errors and associated risk of lack of efficacy of leuprorelin-containing depot-injections. For further background, see [PRAC minutes June 2019](#) and [PRAC minutes November 2019](#)¹⁰.

Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment report issued by the Rapporteurs.
- The PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/317693/2019 Rev 2](#)).

3.3. Procedures for finalisation

3.3.1. Fluorouracil and related substances: capecitabine - CAPECITABINE ACCORD (CAP); CAPECITABINE MEDAC (CAP); CAPECITABINE TEVA (CAP); ECANSYA (CAP); XELODA (CAP); NAP flucytosine (NAP); 5-fluorouracil (5-FU) (NAP); tegafur (NAP); tegafur, gimeracil, oteracil – TEYSUNO (CAP) - EMEA/H/A-31/1481

Applicants: Accord Healthcare Limited (Capecitabine Accord), Krka, d.d., Novo mesto (Ecansya), Medac Gesellschaft für klinische Spezialpräparate mbH (Capecitabine medac), Nordic Group B.V. (Teysono), Roche Registration GmbH (Xeloda), Teva B.V. (Capecitabine Teva), various

PRAC Rapporteur: Jean-Michel Dogné; PRAC Co-rapporteur: Martin Huber

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

Background

A referral procedure under Article 31 of Directive 2001/83/EC for fluorouracil-, capecitabine- and tegafur-containing medicines for systemic use is to be concluded. This referral procedure was initiated in order to review the genotyping and phenotyping methods as well as their availability across the EU for the detection of dihydropyrimidine dehydrogenase (DPD) deficiency responsible for severe and fatal toxicity. The procedure also reviewed the value of the existing screening methods in identifying patients at increased risk of severe side effects as well as the need for updating existing recommendations for pre-treatment evaluation of DPD activity in patients to receive treatment with 5-fluorouracil (5-FU) or related substances. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes March 2019](#), [PRAC minutes July 2019](#), [PRAC minutes October 2019](#)¹¹ and [PRAC minutes December 2019](#)¹².

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

¹⁰ Held 28 – 31 October 2019

¹¹ Held 30 September – 03 October 2019

¹² Held 25-28 November 2019

The PRAC considered the totality of the data submitted during the review in relation to the risk of toxicity associated with DPD deficiency and to the different screening methods currently available to identify patients with DPD deficiency. These data included the responses submitted by the MAHs in writing, an analysis of EudraVigilance data by EMA, third parties' interventions, as well as the outcome of the consultation with the ad-hoc inter-Committee Scientific Advisory Group on Oncology ([SAG-O](#)) and the Pharmacogenomics Working Party ([PgWP](#)).

The PRAC confirmed the current knowledge that the use of 5-FU for systemic use and related substances in patients with DPD deficiency is associated with an increased risk of toxicity.

The PRAC concluded that the benefit-risk balance of 5-FU (intravenous (IV)) and related substances capecitabine, tegafur and flucytosine is negative in patients with complete DPD deficiency and confirmed that these medicinal products should be contraindicated in patients with known complete DPD deficiency. The PRAC also concluded that patients with partial DPD deficiency should be treated with an adjusted starting dose.

To minimise the risk of increased toxicity, the PRAC recommended that DPD deficiency testing is conducted before initiation of treatment. The PRAC considered genotyping and phenotyping by evaluation of blood uracil levels tests as being currently the most suitable methods to identify patients with DPD deficiency. Although both methods have limitations, the PRAC agreed that the product information of 5-FU (IV), capecitabine and tegafur-containing products should provide information on these two testing methodologies together with a guidance to consider applicable clinical guidelines.

For patients requiring treatment with flucytosine, the PRAC considered that pre-treatment DPD testing would not be compatible with the need for immediate treatment required for systemic yeast and fungal infections and therefore agreed that pre-treatment testing for DPD deficiency is not required.

Taking into account the low systemic availability of 5-FU after topical application, the PRAC concluded that the benefit-risk balance of topical 5-FU formulations remains unchanged in all authorised indications but that information on the risk of toxicity in patients with DPD deficiency in case of systemic exposure should be introduced in the product information.

The PRAC concluded that the benefit-risk balance of 5-FU- and related substances capecitabine-, tegafur- and flucytosine-containing products remains favourable subject to the agreed amendments to the product information.

Finally, the PRAC encouraged MAHs and other relevant stakeholders, including academia, to perform further research focussing on current gaps and uncertainties in knowledge.

Summary of recommendation(s)/conclusions

- The PRAC adopted a recommendation to vary¹³ the terms of the marketing authorisation(s) for medicinal products containing 5-FU or related substances capecitabine, flucytosine and tegafur to be considered by CHMP for an opinion – see EMA Press Release ([EMA/125891/2020](#)) entitled 'New testing and treatment recommendations for fluorouracil, capecitabine, tegafur and flucytosine' published on 13 March 2020.

¹³ Update of SmPC sections 4.3 and 4.4 for 5-FU (IV)-, capecitabine- and tegafur-containing products as well as for flucytosine-containing products. Update of section 4.4 for topical 5-FU (5%)- and topical 5-FU (0.5%)-containing products. The package leaflets are updated accordingly

- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) for 5-FU (IV)-, capecitabine- and tegafur-containing products on pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity as well as a [DHPC](#) for flucytosine-containing products on the updated recommendations for the use in patients with DPD deficiency along with communication plans for their distribution.

Post-meeting note: the press release entitled 'EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine' ([EMA/229267/2020](#)) representing the opinion adopted by the CHMP was published on the EMA website on 30 April 2020.

3.4. Re-examination procedures¹⁴

None

3.5. Others

None

4. Signals assessment and prioritisation¹⁵

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

- 4.2.1. Amitriptyline (NAP); bupropion (NAP); citalopram (NAP); desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), YENTREVE (CAP), XERISTAR (CAP), NAP; escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); milnacipran (NAP); mirtazapine (NAP); naltrexone, bupropion – MYSIMBA (CAP); paroxetine (NAP); sertraline (NAP); trazodone (NAP); venlafaxine (NAP); vortioxetine – BRINTELLIX (CAP)

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

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of post-partum haemorrhage

EPITT 19552 – New signal

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

Background

¹⁴ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

¹⁵ 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

Amitriptyline, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, trazodone, venlafaxine and vortioxetine are anti-depressants indicated, among other indications, for the treatment of depression. Mysimba (naltrexone/bupropion) is a centrally authorised product indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial body mass index (BMI) of $\geq 30 \text{ kg/m}^2$ (obese) or $\geq 27 \text{ kg/m}^2$ (overweight) in the presence of one or more weight-related co-morbidities.

The exposure for bupropion-containing products is estimated to have been more than 145.9 million patient exposures worldwide, in the period from 1991 to 2018. The exposure for citalopram-containing products is estimated to have been more than 154.3 million patients worldwide, in the period from first authorisation in 1989 to 2016. The exposure for duloxetine-containing products is estimated to have been more than 32.4 million patient-years worldwide, in the period from first authorisation in 2004 to 2017. The exposure for escitalopram-containing products is estimated to have been more than 402.7 million patients worldwide, in the period from first authorisation in 2001 to 2016. The exposure for fluoxetine is estimated to have been more than 121.6 million patient-years worldwide, in the period from first authorisation in 1986 to 2017. The exposure fluvoxamine is estimated to have been more than 1.56 million patient-years worldwide, in the period from first authorisation in 1983 to 2017. The exposure for milnacipran is estimated to have been more than 3.5 million patient-years worldwide, in the period from first authorisation in 1966 to 2018. The exposure for mirtazapine is estimated to have been more than 21.8 million patient-years worldwide, in the period from first authorisation in 1994 to 2018. The exposure for paroxetine is estimated to have been more than 400 million patient treatments, in the period from first authorisation in 1990 to 2017. The exposure for sertraline is estimated to have been more than 110.5 million patient-years worldwide, in the period from first authorisation in 1990 to 2017. The exposure for venlafaxine is estimated to have been more than 73 million patient-years worldwide, in the period from first authorisation in 1993 to 2017. The exposure for vortioxetine is estimated to have been more than 5.3 million patient-years worldwide, in the period from first authorisation in 2013 to 2019.

Following the publication in BMJ on the 'use of antidepressants near delivery and risk of postpartum hemorrhage' by *Palmsten et al.*¹⁶, a signal of post-partum haemorrhage was identified by Sweden. Sweden as the lead Member State (LMS) for venlafaxine, escitalopram and citalopram confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC considered the available evidence from the study by *Palmsten et al* discussing the link between postpartum haemorrhage with several antidepressant medicines including selective serotonin reuptake inhibitors (SSRIs) and the plausible biological mechanism between bleeding events, which are a known risk of SSRIs. The PRAC agreed that the signal warranted further investigation and recommended that the PRAC Rapporteur performs a review of the available literature.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

¹⁶ Palmsten K, Hernandez-Diaz S, Huybrechts KF, et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: Cohort study of low income women in the United States. *BMJ* 2013;347:f4877

- The PRAC Rapporteur should further evaluate the evidence on the signal via a systematic review of the literature.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Lopinavir, ritonavir – ALUVIA (Art 58¹⁷), KALETRA (CAP), LOPINAVIR/RITONAVIR MYLAN (CAP); NAP

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Aluvia, Kaletra), Mylan S.A.S (Lopinavir, Ritonavir Mylan), various

PRAC Rapporteur: Adrien Inoubli

Scope: Signal of adrenal dysfunction in infants

EPITT 19527 – New signal

Lead Member State(s): FR

Background

Lopinavir is an inhibitor of the human immunodeficiency virus-1 (HIV-1) and HIV-2 proteases. Aluvia, Kaletra and Lopinavir/ritonavir Mylan (lopinavir/ritonavir) are centrally authorised products indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults, adolescents and children.

The exposure for lopinavir/ritonavir-containing products is estimated to have been more than 7.2 million patient-years worldwide, in the period from first authorisation in 2001 to 2018.

Following the publication in by *Kariyawasam et al.*¹⁸, a signal of adrenal dysfunction in infants was identified by EMA. France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of adrenal dysfunction in infants and agreed that this signal warranted further investigation. The PRAC agreed to request a cumulative review of cases of adrenal dysfunction.

The PRAC appointed Adrien Inoubli as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Kaletra (lopinavir/ritonavir) should submit to the EMA, within 60 days, a cumulative review of cases of adrenal dysfunction reported in the post-marketing setting and in clinical trials with lopinavir/ritonavir in infants and children outside the concomitant use of glucocorticoids.
- The authors of the study by *Kariyawasam et al* are invited to provide responses to a list of questions (LoQ) agreed by the PRAC within 60 days.

¹⁷ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

¹⁸ Kariyawasam D et al. Lopinavir-Ritonavir Impairs Adrenal Function in Infants. Clin Infect Dis. 2019 Oct 21. pii: ciz888. doi: 10.1093/cid/ciz888

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

4.2.3. Interferon alfa-2a (NAP); interferon alfa-2b - INTRONA (CAP); peginterferon alfa-2a – PEGASYS (CAP); peginterferon alfa-2b - PEGINTRON (CAP), VIRAFERONPEG (CAP)

Applicant(s): Merck Sharp & Dohme B.V. (IntronA, PegIntron, ViraferonPeg); Roche Registration GmbH (Pegasys), various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of neuromyelitis optica spectrum disorder

EPITT 19532 – New signal

Lead Member State(s): BE, NL, SE

Background

Interferon alfa-2a, peginterferon alfa-2a, interferon alfa-2b and peginterferon alfa-2b are recombinant human interferons. IntronA (interferon alfa-2b), Pegasys (peginterferon alfa-2a), PegIntron and ViraferonPeg (peginterferon alfa-2b) are centrally authorised products indicated, subject to certain conditions, for the treatment of chronic hepatitis B, chronic hepatitis C, treatment of patients with hairy cell leukaemia, adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour and malignant melanoma.

The exposure for interferon alfa-2a-containing products is estimated to have been more than 962 thousand patients worldwide, in the period from first authorisation in 1986 to 2017. The exposure for interferon alfa-2b-containing products is estimated to have been more than 1.18 million patient-years worldwide, in the period from first authorisation in 2000 to 2016. The exposure for peginterferon alfa-2a-containing products is estimated to have been more than 3.1 million patients worldwide, in the period from first authorisation in 2001 to 2017. The exposure for peginterferon alfa-2b-containing products is estimated to have been more than 2.3 million patient-years worldwide, in the period from first authorisation in 2000 to 2019.

During routine signal detection activities, a signal of neuromyelitis optica was identified by the UK, based on 7 cases retrieved from EudraVigilance and from the UK adverse drug reactions (ADR) database. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence from case reports in EudraVigilance, the UK ADR database and from the literature, the PRAC agreed that the signal warranted further investigation and agreed to request further information from the MAHs.

The PRAC appointed Ulla Wändel Liminga as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for IntronA (interferon alfa-2b), PegIntron (peginterferon alfa-2b), ViraferonPeg (peginterferon alfa-2b), Pegasys (peginterferon alfa-2a) and for interferon alfa-2a-containing product(s) should submit to the EMA, within 90 days, a cumulative

review of cases of neuromyelitis optica spectrum disorder and related terms like optic neuritis and transverse myelitis from all sources. The MAHs should also discuss the need for any amendments to the product information and/or the RMP and make a proposal as applicable.

- A 90-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. Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP;
Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP);
Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP); imipramine (NAP); nortriptyline (NAP); trimipramine (NAP);
Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP); phenelzine (NAP); selegiline (NAP); tranylcypromine (NAP);
Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); lithium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP);
Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan (NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP);
Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP); tropisetron (NAP);
Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP)
-

Applicant(s): Accord Healthcare S.L.U. (Palonosetron Accord), Camurus AB (Buvidal), Eli Lilly Nederland B.V. (Cymbalta, Duloxetine Lilly, Xeristar, Yentreve), Helsinn Birex Pharmaceuticals (Aloxi, Akynzeo), Indivior Europe Limited (Suboxone), Kyowa Kirin Holdings B.V. (Sancuso), L. Molteni & C. dei Fratelli Alitti (Sixmo), Mundipharma Corporation (Nyxoid), Mylan S.A.S (Duloxetine Mylan), Orexo AB (Zubsolv), Zentiva k.s. (Duloxetine Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of drug-drug interaction with serotonergic drugs leading to serotonin syndrome

EPITT 19475 – Follow-up to November 2019

Background

For background information, see [PRAC minutes November 2019](#)¹⁹.

The Rapporteur assessed the cumulative review of EudraVigilance data on the signal of drug-drug interaction with serotonergic drugs leading to serotonin syndrome provided by

¹⁹ Held 28-31 October 2019

the EMA.

Discussion

Having considered the available evidence in EudraVigilance and in the literature on the signal of serotonin syndrome in association with the interaction between buprenorphine-containing products and other serotonergic drugs, the PRAC agreed that there is sufficient evidence for establishing a causal association. Therefore, the PRAC agreed to request comments from MAHs on a proposal to update their product information.

Summary of recommendation(s)

- The MAHs for Sixmo (buprenorphine) and Suboxone (buprenorphine/naloxone) should submit to EMA, within 30 days, comments on the proposed updates of the product information.

4.3.2. Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP); dienestrol (NAP); diethylstilbestrol (NAP); estradiol (NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); methallenestril (NAP); moxestrol (NAP); promestriene (NAP); tibolone (NAP)

Applicant(s): Pfizer Europe MA EEIG (Duavive), various

PRAC Rapporteur: Menno van der Elst

Scope: New information on the known risk of breast cancer

EPITT 19482 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

The Rapporteur assessed the recently published meta-analysis²⁰ to determine whether the current product information of hormone replacement therapy (HRT)-containing products needs to be updated regarding the risk of breast cancer.

Discussion

The PRAC considered that the results of the meta-analysis provide sufficient evidence to warrant updating the product information of HRT-containing products and agreed to request comments from MAHs on the proposed updates of the product information.

Summary of recommendation(s)

- The MAHs for Duavive (conjugated oestrogens/bazedoxifene), tibolone-containing product(s), HRT products containing oestrogens only and combined oestrogen-progestagen and vaginally applied oestrogen HRT-products of which the systemic exposure remains within postmenopausal range should submit to EMA, within 30 days, comments on the proposal to update the product information.

²⁰Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019;394(10204):1159-1168

4.3.3. Immune checkpoint inhibitors:
atezolizumab – TECENTRIQ (CAP) - EMEA/H/C/004143/SDA/018.1; avelumab – BAVENCIO (CAP) - EMEA/H/C/004338/SDA/005; cemiplimab – LIBTAYO (CAP) EMEA/H/C/004844/SDA/004.1; durvalumab – IMFINZI (CAP) EMEA/H/C/004771/SDA/003.1; ipilimumab – YERVOY (CAP) EMEA/H/C/002213/SDA/039; nivolumab – OPDIVO (CAP) EMEA/H/C/003985/SDA/039; pembrolizumab - KEYTRUDA (CAP) EMEA/H/C/003820/SDA/024

Applicant(s): AstraZeneca AB (Imfinzi), Bristol-Myers Squibb Pharma (Opdivo), Bristol-Myers Squibb Pharma EEIG (Yervoy), Merck Europe B.V. (Bavencio), Merck Sharp & Dohme B.V. (Keytruda), Regeneron Ireland U.C. (Libtayo), Roche Registration GmbH (Tecentriq)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of tuberculosis

EPITT 19464 – Follow-up to January 2020

Background

For background information, see [PRAC minutes January 2020](#).

The MAHs for Imfinzi (durvalumab), Libtayo (cemiplimab) and Tecentriq (atezolizumab) replied to the request for information on the signal of tuberculosis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative reviews and comments provided by the MAHs of Bavencio (avelumab), Imfinzi (durvalumab), Keytruda (pembrolizumab), Libtayo (cemiplimab), Opdivo (nivolumab), Tecentriq (atezolizumab) and Yervoy (ipilimumab), the PRAC agreed that the risk of tuberculosis should be further monitored via routine pharmacovigilance and that the product information of Imfinzi (durvalumab), Libtayo (cemiplimab) and Tecentriq (atezolizumab) should be updated to highlight advice to rule out infectious and disease-related aetiologies in patients with suggestive symptoms.

Summary of recommendation(s)

- The MAHs for Imfinzi (durvalumab), Libtayo (cemiplimab) and Tecentriq (atezolizumab) should submit to the EMA, within 60 days, a variation to update the product information²¹ with a warning that infectious and disease-related aetiologies should be ruled out in patients with signs and symptoms suggestive for immune-related pneumonitis.

For the full PRAC recommendation, see [EMA/PRAC/111214/2020](#) published on 06/04/2020 on the EMA website.

²¹ Update of SmPC section 4.4

4.3.4. Mycophenolic acid (NAP); mycophenolate mofetil - CELLCEPT (CAP) - EMEA/H/C/000082/SDA/040, MYCLAUSEN (CAP), MYCOPHENOLATE MOFETIL TEVA (CAP), MYFENAX (CAP), NAP

Applicant(s): Passauer Pharma GmbH (Myclausen), Roche Registration GmbH (Cellcept), Teva B.V. (Mycophenolate Mofetil Teva, Myfenax), various

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of posterior reversible encephalopathy syndrome (PRES)

EPITT 19473 – Follow-up to November 2019

Background

For background information, see [PRAC minutes November 2019](#).

The MAHs of the originator medicinal products containing mycophenolic acid and mycophenolate mofetil, Novartis Pharma N.V. and Roche Registration GmbH replied to the request for information on the signal of posterior reversible encephalopathy syndrome (PRES) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative reviews provided by the MAHs, the PRAC agreed that the number of possible cases of PRES with a temporal relationship to mycophenolate mofetil (MMF) or mycophenolic acid (MPA) is low and that the likelihood of a causal relationship between the treatment with MMF/MPA and PRES is not sufficiently strong at the moment. The PRAC agreed that no further regulatory actions were warranted at present.

Summary of recommendation(s)

- The MAHs of mycophenolic acid- and mycophenolate mofetil-containing products should continue to monitor these events as part of routine safety surveillance.

4.3.5. Paroxetine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of microscopic colitis

EPITT 19474 – Follow-up to November 2019

Background

For background information, see [PRAC minutes November 2019](#).

The MAH of the originator paroxetine-containing product, GlaxoSmithKline replied to the request for information on the signal of microscopic colitis and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence in EudraVigilance and in the literature, the PRAC agreed that there is sufficient evidence for a causal relationship between paroxetine and microscopic colitis and agreed that the product information should be updated accordingly.

Summary of recommendation(s)

- The MAHs of paroxetine-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information²².

For the full PRAC recommendation, see [EMA/PRAC/111214/2020](#) published on 06/04/2020 on the EMA website.

- 4.3.6. Thiazide, thiazide-like diuretics and combinations:
bendroflumethiazide (NAP); chlortalidone (NAP); cicletanine (NAP); clopamide (NAP); cyclopenthiiazide (NAP); hydrochlorothiazide (NAP); hydrochlorothiazide, aliskiren – RASILEZ HCT (CAP); hydrochlorothiazide, amlodipine, valsartan - EXFORGE HCT (CAP); hydrochlorothiazide, irbesartan – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); hydrochlorothiazide, telmisartan – ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP); hydrochlorothiazide, valsartan, amlodipine - COPALIA HCT (CAP), DAFIRO HCT (CAP); hydroflumethiazide (NAP); indapamide (NAP); metipamide (NAP); metolazone (NAP); xipamide (NAP)
-

Applicant(s): Actavis group PTC ehf (Actelsar HCT), Bayer AG (Kinzalkomb, PritorPlus), Boehringer Ingelheim International GmbH (MicardisPlus), Krka, d.d., Novo mesto (Ifirmacombi, Tolucombi), Noden Pharma DAC (Rasilez HCT), Novartis Europharm Limited (Copalia HCT, Dafiro HCT, Exforge HCT), Sanofi-Aventis groupe (CoAprovel, Karvezide), Teva B.V. (Irbesartan/Hydrochlorothiazide Teva), Zentiva k.s. (Irbesartan Hydrochlorothiazide Zentiva), various

PRAC Rapporteur: Martin Huber

Scope: Signal of choroidal effusion

EPITT 19468 – Follow-up to December 2019

Background

For background information, see [PRAC minutes December 2019](#)²³.

The MAHs Alliance Pharmaceuticals Ltd, Mylan N.V., Juvisé Pharmaceuticals and Pharmaswiss Česká Republika S.R.O. for originator-thiazide, thiazide-like diuretics and/or combinations replied to the request for information on the signal of choroidal effusion and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, the literature together with the comments submitted by the MAHs, the PRAC agreed that there is sufficient evidence for a causal association between the use of these medicines and the occurrence of choroidal effusion. The PRAC agree that the product information of thiazide and thiazide-like diuretics containing products should be updated accordingly.

Summary of recommendation(s)

²² Update of SmPC section 4.8. The package leaflet is updated accordingly

²³ Held 25-28 November 2019

- The MAHs for thiazide and thiazide-like diuretic-containing products should submit to the EMA or to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update their product information²⁴.

For the full PRAC recommendation, see [EMA/PRAC/111214/2020](#) published on 06/04/2020 on the EMA website.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

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

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

See also Annex I 15.1.

5.1.1. Aripiprazole - EMEA/H/C/005062

Scope: Treatment of schizophrenia, moderate to severe manic episodes in bipolar I disorder with sensor to measure medication adherence

5.1.2. Autologous CD²⁵34⁺ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene - EMEA/H/C/005321, Orphan

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP²⁶

Scope (accelerated assessment): Treatment of metachromatic leukodystrophy (MLD)

5.1.3. Fenfluramine - EMEA/H/C/003933, Orphan

Applicant: Zogenix GmbH

Scope: Treatment of seizures associated with Dravet syndrome in children aged 2 years to 17 years and adults

5.1.4. Lefamulin - EMEA/H/C/005048

Scope: Treatment of community-acquired pneumonia (CAP)

5.1.5. Obiltoximab - EMEA/H/C/005169, Orphan

Applicant: SFL Regulatory Services GmbH

²⁴ Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

²⁵ Cluster of differentiation

²⁶ Advanced therapy medicinal product

Scope: Treatment of inhalational anthrax due to *Bacillus anthracis*

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

See also Annex I 15.2.

5.2.1. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/WS1713/0109; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/WS1713/0083; dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/WS1713/0075; lamivudine, abacavir, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/WS1713/0115

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of updated RMPs (version 2.0 for Kivexa, Trizivir and Ziagen; version 17.0 for Triumeq) in order to remove the additional risk minimisation measure (aRMM) on the education materials for healthcare professionals on abacavir hypersensitivity. Annex II is updated accordingly

Background

Abacavir, lamivudine and zidovudine are nucleoside reverse transcriptase inhibitors (NRTIs). Dolutegravir is a second-generation human immunodeficiency virus (HIV) integrase strand transfer inhibitor (INSTI). Abacavir is indicated, as Ziagen, in antiretroviral combination therapy for the treatment of HIV infection in adults, adolescents and children under certain conditions. Abacavir/lamivudine is indicated, as Kivexa, for the treatment of HIV infection in adults, adolescents and children weighing at least 25 kg. Abacavir/lamivudine/dolutegravir is indicated, as Triumeq, for the treatment of HIV infection in adults and adolescents above 12 years of age weighing at least 40 kg. Abacavir/lamivudine/zidovudine is indicated, as Trizivir, for the treatment of HIV infection in adults.

The PRAC is evaluating a worksharing variation procedure for Ziagen, Kivexa, Triumeq and Trizivir and centrally authorised medicines containing abacavir, abacavir/lamivudine, abacavir/lamivudine/dolutegravir and abacavir/lamivudine/zidovudine respectively, to update the RMPs in order to remove the educational materials for healthcare professionals (HCPs) as additional risk minimisation measure for the identified risk of 'abacavir hypersensitivity reaction'. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes January 2020](#).

Summary of advice

- The RMP (version 2.0) for Kivexa (abacavir/lamivudine), Trizivir (abacavir/lamivudine/zidovudine) and Ziagen (abacavir) and the RMP (version 17.0) for Triumeq (abacavir/lamivudine/dolutegravir) in the context of the variation procedure under evaluation are considered acceptable.
- The PRAC agreed with the proposal to remove the existing educational materials for HCPs as the risk of abacavir hypersensitivity reaction is currently well known to treating physicians and is adequately managed by the current product information and relevant guidelines. As a consequence, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly. In addition,

the PRAC supported the removal of yearly review of suspected cases and instead, recommended to closely monitor cases of hypersensitivity in PSURs. The PRAC confirmed the maintenance of the patient alert card.

5.2.2. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/II/0052

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

Scope: Submission of an updated RMP (version 19.2) in order to update information relating to educational material to include greater emphasis on off label use and the risk of misuse and abuse. In addition, the MAH submitted a synopsis of a protocol for a PASS (as a category 3 study in the RMP) to assess the impact of the updated educational material

Background

Fentanyl is an opioid analgesic interacting primarily with the opioid μ -receptor as a pure agonist with low affinity for the δ - and κ -opioid receptors. It is indicated, as Instanyl, for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

The PRAC is evaluating a type II variation procedure for Instanyl, a centrally authorised medicine containing fentanyl, to update the RMP on key messages to be included in the educational material for prescribers/pharmacists and patients, a discussion on the impact of an access restriction of the medicinal product to some prescribers as well as a synopsis for a PASS to assess the impact of the updated educational material. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation. For further background, see [PRAC minutes December 2019](#)²⁷.

Summary of advice

- The RMP (version 19.6) for Instanyl (fentanyl) in the context of the variation procedure under evaluation is considered acceptable.
- As regards the educational material, the PRAC agreed on the targeted audience (i.e. patient/carer, physician/prescriber and pharmacist) and the updated key elements including the addition of enhanced digital access information. With regards to the proposed QR code linked to digital educational material, the PRAC concluded that both the implementation of the QR²⁸ code on the packaging and/or package leaflet and the specificities of the website/webpage should be decided at national level. In relation to the prescriber definition in the RMP, the PRAC agreed that prescribers should be defined as per on-label guidance and may include oncologists and onco-radiotherapists, anaesthesiologists, pain management specialists, haematologists, palliative care physicians, internal medicine specialists/ internists and GPs. This should be agreed with each National Competent Authority (NCA) of the Member States. In addition, the PRAC supported the inclusion of '6-month periodic report on the Doseguard development status' (LEG 028) in the RMP routine pharmacovigilance activities. Nevertheless, the PRAC considered that the development of the Doseguard device together with the due

²⁷ Held 25-28 November 2019

²⁸ Quick response

date for completion should not be added as an additional risk minimisation measure (aRMM) taking into account that the device is currently authorised and is implemented in the product information. Besides, the PRAC endorsed the PASS synopsis on the assessment of effectiveness of the updated educational materials on prescribers' knowledge and behaviour with respect to the risks associated with the off-label use of Instanyl (fentanyl). The PRAC supported requesting the MAH to submit a variation to the EMA in order to include 'patients at risk of abuse and misuse' to the product information. Finally, the PRAC agreed on the key messages of the educational materials.

5.2.3. Human coagulation factor VIII, human von Willebrand factor - VONCENTO (CAP) - EMEA/H/C/002493/II/0042

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 7) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems' and reflect the completion of study CSLCT-BIO-12-83: a post-marketing study (PMS) to collect long-term data on the haemostatic efficacy of human coagulation factor VIII/von Willebrand factor (FVIII/VWF) complex in patients with von Willebrand Disease (VWD) who require a VWF product to control a bleeding event or as prophylaxis therapy. In addition, the RMP is updated to request a waiver to study Biostate_4001 (listed as a category 3 study in the RMP): a low-interventional multicentre PASS for Voncento (FVIII/VWF) for routine prophylaxis, treatment of bleeding events and/or surgery in male patients with haemophilia A due to feasibility reasons

Background

Human coagulation factor VIII (FVIII) and human von Willebrand factor (VWD) are anti-haemorrhagics and blood coagulation factors. In combination, human coagulation FVIII/human VWD are indicated, as Voncento, for the prophylaxis and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated as well as for the prophylaxis and treatment of bleeding in patients with haemophilia A.

The PRAC is evaluating a type II variation procedure for Voncento, a centrally authorised medicine containing human coagulation FVIII/human VWD, to update the RMP including a request for an exemption to conduct study Biostate_4001: a low-interventional multicentre PASS for Voncento (FVIII/VWF) for routine prophylaxis, treatment of bleeding events and/or surgery in male patients with haemophilia A due to feasibility reasons. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Voncento (FVIII/VWF) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 7.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC agreed that an exemption to conduct study Biostate_4001 is acceptable based on a feasibility report showing difficulties in the recruitment of patients and little

prospect of ever recruiting sufficient patients to provide confirmation of a frequency of occurrence of inhibiting antibodies to FVIII in previously treated haemophilia A patients.

5.2.4. **Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0052**

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP to replace the prospective observational cohort study of Flixabi in patients with Crohn's disease (CD) (SB2-G42-CD), with real-world data from the following studies: 1) PERFUSE: a French cohort study with the primary aim to evaluate the persistence of Flixabi (infliximab) treatment over one year; 2) CREDIT: a nationwide German inflammatory bowel disease (IBD) registry: a long term observation of IBD patients; 3) CEDUR: Czech register of IBD patients on biological therapy

Background

Infliximab is a chimeric human-murine monoclonal antibody that binds to tumour necrosis factor alfa (TNF α). Infliximab is indicated, as Flixabi, for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis subject to certain conditions.

The PRAC is evaluating a type II variation procedure for Flixabi, a centrally biosimilar authorised medicine containing infliximab, to update the RMP to replace the prospective observational cohort study of Flixabi in patients with Crohn's disease (SB2-G42-CD), with real-world data from several studies, namely, PERFUSE: a French cohort study with the primary aim to evaluate the persistence of Flixabi (infliximab) treatment over one year; CREDIT: a nationwide German inflammatory bowel disease (IBD) registry: a long term observation of IBD patients; and CEDUR: Czech register of IBD patients on biological therapy. The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Flixabi (infliximab) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 11.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the CEDUR and CREDIT IBD registries are likely to provide clinical data of interest for the remaining safety concerns of comparable relevance as for study SB2-G42-CD. However, the PRAC did not support the inclusion of the CEDUR register into the RMP.

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

See Annex I 15.3.

6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

6.1.1. Cobicistat - TYBOST (CAP) - PSUSA/00010081/201908

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. It is indicated, as Tybost, as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tybost, a centrally authorised medicine containing cobicistat, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Tybost (cobicistat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning to not initiate atazanavir/cobicistat during pregnancy, and to switch to an alternative regimen for women who become pregnant during therapy with atazanavir/cobicistat. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.

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. Dronedarone - MULTAQ (CAP) - PSUSA/00001180/201907

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

²⁹ Update of SmPC sections 4.2, 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Dronedarone is a multichannel blocker inhibiting the potassium currents. It is indicated, as Multaq, for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Multaq, a centrally authorised medicine containing dronedarone and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Multaq (dronedarone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include information on the drug interaction between dronedarone and with medicinal products metabolised by CYP 3A4³⁰ and P-glycoprotein (P-gp) substrate, namely rivaroxaban, apixaban and edoxaban. Therefore, the current terms of the marketing authorisation(s) should be varied³¹.
- In the next PSUR, the MAH should closely monitor the possible drug-drug interaction of dronedarone and rivaroxaban.

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. Submission of PSURs for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended is not required any longer and the EURD list should be updated accordingly.

6.1.3. Linacotide - CONSTELLA (CAP) - PSUSA/00010025/201908

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Linacotide is a guanylate cyclase-C receptor agonist (GCCA), indicated as Constella, for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Constella, a centrally authorised medicine containing linacotide and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Constella (linacotide) in the approved indication(s) remains unchanged.

³⁰ Cytochrome P450 3A4

³¹ Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Nevertheless, the product information should be updated to include urticaria as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³².
- In the next PSUR, the MAH should provide information on the amount of prescribed underdose as an effect of the regional label's dosage instructions in Japan, as well as a summary of efficacy-related information both from non-interventional studies and from the literature.
- The MAH should submit to the EMA, within 60 days, the study protocol and study report of the Truven MarketScan study³³. In addition, a detailed review of all cases of intestinal perforation should be provided.

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. Panobinostat - FARYDAK (CAP) - PSUSA/00010409/201908

Applicant: Secura Bio Limited

PRAC Rapporteur: Sofia Trantza

Scope: Evaluation of a PSUSA procedure

Background

Panobinostat is a histone deacetylase (HDAC) inhibitor, indicated as Farydak, in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Farydak, a centrally authorised medicine containing panobinostat and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Farydak (panobinostat) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend a warning on carcinogenesis and mutagenesis. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.

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

³² 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

³³ Truven MarketScan claims database used to assess the potential association between linaclotide and gastrointestinal (GI) perforation

³⁴ Update of SmPC section 5.3. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.5. Patisiran - ONPATTRO (CAP) - PSUSA/00010715/201908

Applicant: Alnylam Netherlands B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Patisiran is a double-stranded small interfering ribonucleic acid (siRNA), indicated as Onpattro, for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Onpattro, a centrally authorised medicine containing patisiran and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Onpattro (patisiran) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to update the existing warning on infusion related reactions to include hypotension and syncope. In addition, syncope should be added as an undesirable effect with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁵.
- In the next PSUR, the MAH should provide a review and discussion on fatal cases including cases of sudden death, a cumulative review of pruritus and pyrexia, a cumulative review of events reported following infusion in the home setting and a discussion any new cases of urticaria. In addition, the MAH should provide cumulative reviews of cases of cardiac failure, of cerebrovascular accidents, a review on capillary leak syndrome, as well as reviews on cytokine release syndrome and anaphylactoid reactions.

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. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201909

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

Background

Pembrolizumab is a humanised monoclonal antibody and antineoplastic agent indicated, as Keytruda, in monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, adjuvant treatment of adults with stage III melanoma and lymph node

³⁵ 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

involvement who have undergone complete resection, for the first line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) under certain conditions, for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 under certain conditions, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) under certain conditions, for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy. It is also indicated as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥ 1 and for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS) and progressing on or after platinum-containing chemotherapy, and in combination with axitinib for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Keytruda, a centrally authorised medicine containing pembrolizumab and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Keytruda (pembrolizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to update the existing warning on 'other immune-related adverse reactions' to add myelitis. In addition, glomerulonephritis should be added as an undesirable effect as a footnote to nephritis, and gastrointestinal ulceration and myelitis should be added as undesirable effects with a frequency 'uncommon' and 'rare' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should provide a further evaluation of the risk of transient acantholytic dermatosis and a review of cases of enteritis. In addition, the MAH should provide detailed reviews of cases of gastritis, of cases of vestibular syndrome, inner ear disorders and vestibulocochlear nerve injury, of cases of bronchial hyper-reactivity, of cases of lupus cutaneous and erythematous as well as a comprehensive review of cases of agranulocytosis. Furthermore, the MAH should discuss new information on the signal of cholangitis, as well as discuss whether the frequency of adverse drug reactions (ADRs) is increased in patients on concomitant cancer treatments (protein kinase inhibitors).

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. Romiplostim - NPLATE (CAP) - PSUSA/00002660/201907

Applicant: Amgen Europe B.V.

³⁶ 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

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Romiplostim is an Fc-peptide fusion protein (peptibody) indicated, as Nplate, for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Nplate, a centrally authorised medicine containing romiplostim and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Nplate (romiplostim) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to further describe the available data in immunogenicity. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.
- In the next PSUR, the MAH should provide a cumulative review of cases of interstitial lung disease and pulmonary fibrosis.

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. Teduglutide - REVESTIVE (CAP) - PSUSA/00009305/201908

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

Background

Teduglutide is an analogue of human glucagon-like peptide-2 (GLP-2), indicated as Revestive, for the treatment of patients aged 1 year and above with short bowel syndrome (SBS).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Revestive, a centrally authorised medicine containing teduglutide and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Revestive (teduglutide) in the approved indication(s) remains unchanged.

³⁷ 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

- Nevertheless, the product information should be updated to include a warning on the risk of fluid imbalance and dehydration. Therefore, the current terms of the marketing authorisation(s) should be varied³⁸.

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

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

See Annex I 16.2.

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

See also Annex I 16.3.

6.3.1. Brivudine (NAP) - PSUSA/00000434/201907

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Brivudine is an antiviral drug indicated for the early treatment of acute herpes zoster in immunocompetent adults.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of brivudine-containing product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a contraindication and a warning on the interaction between brivudine and fluoropyrimidines due to the potential fatal toxicity of fluoropyrimidines if administered shortly before or at the same time with brivudine or used within 4 weeks after the end of treatment with brivudine. In addition, the PRAC recommended a prescriber checklist as well as a patient alert card as conditions to the marketing authorisation(s) for brivudine containing product(s). Therefore, the current terms of the marketing authorisation(s) should be varied³⁹.
- The PRAC agreed on the content of a direct healthcare professional communication ([DHPC](#)) along with a communication plan for its distribution.

³⁸ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁹ Update of SmPC sections 4.3, 4.4, 4.5 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

- In the next PSUR, the MAHs should provide cumulative reviews of cases of Kounis-syndrome, alveolitis, delirium, drug-induced liver injury (DILI) and drug-drug interactions.
- The MAHs should submit as a work sharing variation to the relevant National Competent Authorities (NCAs) of the Member States, within 90 days, consisting of a detailed review of all cases of nervous system disorders and psychiatric disorders as well as a detailed review of all cases of skin and sub-cutaneous tissue disorders. The MAHs should propose an update of the product information as warranted.

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

6.3.2. Busulfan (NAP) - PSUSA/00000464/201907

Applicant(s): various

PRAC Lead: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Busulfan is a cytotoxic agent indicated for the conditioning treatment prior to haemopoietic progenitor cell transplantation in patients when the combination of high-dose busulfan and cyclophosphamide is considered the best available option, for the palliative treatment of the chronic phase of chronic myeloid leukaemia, in producing prolonged remission in polycythaemia vera and in selected cases of essential thrombocythaemia and myelofibrosis.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of busulfan-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the interaction between busulfan and deferasirox. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.
- In the next PSUR, the MAH should closely monitor cases of serious cutaneous adverse reactions (SCARs).

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to the 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.

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

6.3.3. Ropinirole (NAP) - PSUSA/00002661/201907

Applicant(s): various

PRAC Lead: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Ropinirole is a D2/D3 dopamine agonist indicated for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS).

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of ropinirole-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on risk factors of dopamine agonist withdrawal syndrome (DAWS). Therefore, the current terms of the marketing authorisation(s) should be varied⁴¹.
- In the next PSUR, the MAHs should provide a comprehensive review of camptocormia, and discuss the need for updating the product information as warranted. The MAHs should also provide a comprehensive review of serotonin syndrome. In addition, the MAHs should provide new information regarding risk factors of DAWS and propose changes to the product information as appropriate.

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

6.4. Follow-up to PSUR/PSUSA procedures

None

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴²

See Annex I 17.1.

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

See also Annex I 17.2.

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

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

⁴³ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

7.2.1. Neratinib - NERLYNX (CAP) - EMEA/H/C/004030/MEA 002.1

Applicant: Pierre Fabre Medicament

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002 [protocol for study PUMA-NER-6202: a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage epidermal growth factor receptor 2 + (HER2+) breast cancer treated with neratinib and intensive loperamide prophylaxis versus neratinib and intensive loperamide prophylaxis plus a bile acid sequestrant in the first month of treatment [final study results expected in December 2021]] as per the request for supplementary information (RSI) adopted in July 2019

Background

Neratinib is an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) that blocks mitogenic growth factor signal transduction. It is indicated, as Nerlynx a centrally authorised medicine, for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

As part of the RMP of Nerlynx (neratinib), the MAH is requested to conduct a randomised study to characterise the incidence and severity of diarrhoea in patients with early stage HER2+ breast cancer treated with neratinib. The MAH was requested to submit a revised protocol for study PUMA-NER-6202 for the evaluation of the risk of diarrhoea which was assessed by the Rapporteur. The PRAC is requested to provide advice to CHMP on the protocol submitted by the MAH. For further background, see [PRAC minutes July 2019](#).

Summary of advice

- The MAH should submit to EMA, within 60 days, a revised protocol with an amended definition of intention-to-treat (ITT) population, including a systematic collection of the reason for treatment, a collection of gastrointestinal adverse events (AEs) other than diarrhoea. More information is also needed on the handling of missing data, randomisation methods, clinical difference for the patient reported outcomes, sample size of the control cohort and limitations of the research methods.

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁴

7.3.1. Rivaroxaban – XARELTO (CAP) - EMEA/H/C/PSR/S/0024

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Results for an observational post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales

⁴⁴ In accordance with Article 107p-q of Directive 2001/83/EC

Background

Rivaroxaban is a direct factor Xa inhibitor. It is indicated, as Xarelto a centrally authorised medicine, under certain conditions for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers and for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. It is also indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. In addition, it is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

As a condition to the marketing authorisation(s) ([Annex II-D](#)), the MAH was required to conduct a non-interventional post-authorisation safety specialist cohort event monitoring study (SCEM) to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales. In accordance with Article 107p of Directive 2001/83/EC, the MAH Bayer AG submitted the final study report to the EMA. The PRAC is responsible for assessing the final study results.

Summary of recommendation(s) and conclusions

- Based on the review of the final report of the non-interventional PASS entitled 'an observational post-authorisation safety SCEM to monitor the safety and utilisation of Xarelto (rivaroxaban) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales', the PRAC considered that the benefit-risk balance of Xarelto (rivaroxaban) remains positive. As a consequence, the PRAC recommended that the study can be removed from the RMP at the next regulatory opportunity. Regarding the terms of the marketing authorisation(s) for Xarelto (rivaroxaban), no change is recommended at the present time. With the final results from the studies from the PASS programme reflected in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product', further assessment will be undertaken, to review whether the conditions have been fulfilled or not.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁵

See also Annex 1 17.4.

7.4.1. Linaclotide - CONSTELLA (CAP) - EMEA/H/C/002490/II/0043

Applicant: Allergan Pharmaceuticals International Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final report from study linaclotide utilisation study in selected European populations (listed as a category 3 study in the RMP): a drug utilisation study (DUS) to address the following safety concerns: potential for off-label use and abuse/excessive use, use in pregnancy and lactation and male patients as well as off-label

⁴⁵ 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

use and use in males and in pregnant female patients

Background

Linacotide is a guanylate cyclase-C receptor agonist indicated, as Constella a centrally authorised medicine, for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

As stated in the RMP of Constella (linaclotide), the MAH conducted a non-imposed non-interventional PASS entitled 'linaclotide utilisation study in selected European populations to assess the potential for off-label use and abuse/excessive use, the extent of use in pregnancy and lactation and to assess the extent of off-label use and the extent of use in males and in pregnant females'. The Rapporteur assessed the MAH's final study report together with the MAH's responses to requests for supplementary information (RSI). For further background, see [PRAC minutes December 2019](#)⁴⁶ and [PRAC minutes February 2020](#).

Summary of advice

- Based on the available data, the MAH's responses to the RSIs and the Rapporteur's review, the PRAC acknowledged the high off-label use shown by data from the drug utilisation study (DUS). The PRAC considered the off-label use as self-limiting (trial and error) and in light of the severity of the related adverse drug reactions (ADRs), no further action was deemed necessary for the time being. The PRAC advised to finalise the ongoing variation assessing the final study report and that the variation could be recommended for approval.

7.4.2. Riociguat - ADEMPAS (CAP) - EMEA/H/C/002737/II/0030, Orphan

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Submission of the final report for study 16657, EXPERT (EXPosurE Registry RiociguaT in patients with pulmonary hypertension) (listed as a category 3 study in the RMP) to collect information about the long-term use of Adempas (riociguat) in real clinical practice. The RMP (version 7.1) is updated accordingly

Background

Riociguat is a stimulator of soluble guanylate cyclase (sGC) indicated, as Adempas a centrally authorised medicine, for the treatment of adult patients with WHO⁴⁷ functional class (FC) II to III to improve exercise capacity, subject to certain conditions. It is also indicated in monotherapy or in combination with endothelin receptor antagonists for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO FC II to III to improve exercise capacity.

As stated in the RMP of Adempas (riociguat), the MAH conducted a global, multicentre, prospective, uncontrolled, non-interventional cohort study in patients with PAH to collect information about the long-term use of Adempas (riociguat) in real clinical practice. The Rapporteur assessed the MAH's final study report together with the MAH's responses to the

⁴⁶ Held 25-28 November 2019

⁴⁷ World Health Organization

request for supplementary information (RSI). For further background, see [PRAC minutes November 2019](#)⁴⁸.

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC supported the conclusions reached on the final study results. The estimated study size was reached and based on the reported adverse events (AE)/serious AEs (SAEs), the safety data was in line with the known safety profile of riociguat in the approved indications and no new identified safety signal was identified. In relation to the proposed revisions to the RMP (version 7.2), the PRAC agreed that at this stage all safety concerns could be removed as they have all been sufficiently characterised by the EXPERT study and/or no further additional pharmacovigilance activities are considered necessary. Nevertheless, considering their high relevance for the safety profile of Adempas (riociguat), the PRAC considered they should be maintained and closely monitored in future PSURs. Finally, the PRAC advised to finalise the ongoing variation assessing the final study report and that this variation could be recommended for approval.

7.4.3. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0043

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Submission of the final report for study INC424AIC01T (listed as a category 3 study in the RMP): a non-interventional, observational PASS in order to provide real-world safety data on patients with myelofibrosis (MF) who were exposed and non-exposed to ruxolitinib and provide insights into disease management and the safety profile of ruxolitinib. The RMP (version 11.0) is updated accordingly

Background

Ruxolitinib is a Janus associated kinase (JAK) inhibitor, indicated as Jakavi a centrally authorised medicine, for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. It is also indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

As stated in the RMP of Jakavi (ruxolitinib), the MAH conducted a non-imposed non-interventional PASS INC424AIC01T, a non-interventional, observational PASS intended to provide real-world safety data on patients with myelofibrosis who were exposed and non-exposed to Jakavi (ruxolitinib). The Rapporteur assessed the MAH's final study report in addition to the MAH's answers to the request for supplementary information (RSI). For further background, see [PRAC minutes October 2019](#).

Summary of advice

- Based on the available data, the MAH's answers to the RSI and the Rapporteur's review, the PRAC considered the final study results of the study have not changed the benefit risk balance of Jakavi (ruxolitinib) which remains positive. The PRAC agreed that data showed that the concurrent use of ruxolitinib and hematopoietic growth factors was safe

⁴⁸ Held 28 – 31 October 2019

and did not decrease the efficacy of ruxolitinib. Similarly, review of data from concurrent use of ruxolitinib and cytoreductive therapies suggested manageable haematological toxicities. Therefore, the PRAC advised to update the product information⁴⁹ accordingly. With regard to the update of the RMP, the PRAC agreed to remove pharmacodynamic interaction between ruxolitinib and haematopoietic growth factors or combination with cytoreductive therapies as an important potential risk. Finally, the PRAC advised to finalise the ongoing variation assessing the final study report and that this variation could be recommended for approval.

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

See also Annex I 17.5.

7.5.1. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/ANX 006.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Dasabuvir is a direct-acting antiviral indicated, as Exviera, for the treatment of chronic hepatitis C infection.

The MAH had committed to perform a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in the Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)). Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

⁴⁹ Update of SmPC sections 4.4 and 4.5. The PRAC AR is transmitted to the CHMP for adoption of an opinion

7.5.2. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/ANX 005.1

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Elbasvir and grazoprevir are direct-acting antivirals indicated, as Zepatier, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.3. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/ANX 001

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Glecaprevir and pibrentasvir are direct-acting antivirals indicated, as Maviret, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.4. [Ledipasvir, sofosbuvir - HARVONI \(CAP\) - EMEA/H/C/003850/ANX 016.1](#)

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Ledipasvir and sofosbuvir are direct-acting antivirals indicated, as Harvoni, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.5. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/ANX 006.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Ombitasvir and paritaprevir are direct-acting antivirals. Ritonavir is a protease inhibitor. In combination, ombitasvir/paritaprevir/ritonavir is indicated, as Viekirax, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.6. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/ANX 023.1

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Sofosbuvir is a direct-acting antiviral indicated, as Sovaldi, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.7. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/ANX 009.1

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Sofosbuvir and velpatasvir are direct-acting antivirals indicated, as Epclusa, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.5.8. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/ANX 004

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Interim results of DAA-PASS study: a non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy in order to estimate the risk of early HCC recurrence associated with DAA therapy exposure compared to no DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, as required in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on DAAV indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMEA/H/A-20/1438) [final study report expected in Q2 2021]

Background

Sofosbuvir, velpatasvir and voxilaprevir are direct-acting antivirals indicated, as Vosevi, for the treatment of chronic hepatitis C infection.

The MAH committed to perform a joint non-interventional imposed study on recurrence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients after direct-acting antiviral (DAA) therapy according to the conditions included in Annex II of the marketing authorisation, further to the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 ([EMEA/H/A-20/1438](#)) completed in 2016. Interim results of the study were assessed by the Rapporteur for PRAC review.

Summary of advice

- The PRAC discussed the interim results and noted that the level of recruitment is much lower than expected, leading to study feasibility issues.
- The MAH should submit to EMA, within 30 days, proposed amendments to the protocol via a procedure under Article 107o of Directive 2001/83/EC for further assessment at PRAC.

7.6. Others

See also Annex I 17.6.

7.6.1. Melatonin - SLENYTO (CAP) - EMEA/H/C/004425/REC 002

Applicant: RAD Neurim Pharmaceuticals EEC SARL

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: First annual French 'recommandation temporaire d'utilisation (RTU)' report on special temporary recommendation of use for Circadin (melatonin) 2-6 mg in the autism spectrum disorder (ASD) and neurogenetic 6-18 year old population for the period from October 2015 to July 2019

Background

Melatonin is a hormone that regulates circadian rhythms and sleep-wake cycles. It is indicated, as Slenyto, for the treatment of insomnia in children and adolescents aged 2-18 with autism spectrum disorder (ASD) and/or Smith-Magenis syndrome.

As an outcome of a variation (II/10) finalised in December 2019, the MAH committed to submit annual reports on the French 'recommandation temporaire d'utilisation (temporary recommendation for use (RTU))'. The PRAC provided advice to the CHMP on this report. For further background, see [PRAC minutes September 2019](#) and [PRAC minutes November 2019](#)⁵⁰.

Summary of advice

- Based on the available data and the Rapporteur's review, the PRAC advised to update of the product information to reflect the adverse reactions reported in children (insomnia, agitation, depression, poor quality sleep, nightmares, abdominal pain, dry mouth, nausea, dermatitis, eczema, peripheral swelling and halitosis). Therefore, the PRAC advised to request the MAH to submit to EMA, a variation to update the product information accordingly. The MAH should also maintain the provision of annual reports and a final report.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

⁵⁰ Held 28 – 31 October 2019

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Olanzapine - OLANZAPINE APOTEX (CAP) - EMEA/H/C/001178/II/0037

Applicant: Apotex Europe BV

PRAC Rapporteur: Kimmo Jaakkola

Scope: PRAC consultation on a type II variation updating sections 4.4 and 4.8 of the SmPC in order to add information regarding the risk of metabolic syndrome (MetS) with the use of olanzapine (and all antipsychotics), based on review of the available data from Apotex global safety database, EudraVigilance and literature, on request of CHMP

Background

Olanzapine is an antipsychotic medicine indicated, as Olanzapine Apotex, for the treatment of schizophrenia and for the treatment of moderate to severe manic episode.

A type II variation proposing to update the product information of Olanzapine Apotex (olanzapine) on the risk of metabolic syndrome is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC agreed that metabolic syndrome is a combination of risk factors for cardiovascular diseases and diabetes mellitus which require assessment and treatment of each of these risk factors individually.
- Therefore, the PRAC concurred that the addition of metabolic syndrome in the product information of Olanzapine Apotex (olanzapine) would have no additional value, as the syndrome is well known among physicians and the relevant individual components of metabolic syndrome are adequately described in the current product information.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

11.1.1. Fentanyl⁵¹ (NAP) - NL/H/3915/II/007/G

Applicant(s): Janssen-Cilag B.V. (Durogesic)

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a variation (part of an ongoing grouped variation procedure) on an update section 4.4 of the SmPC on drug dependence and potential for abuse regarding the increased risk of developing tolerance, physical dependence, or psychological dependence to opioids in individuals with a personal or family history of substance abuse or mental illness, on request of the Netherlands

Background

Fentanyl is an opioid analgesic indicated for the management of severe chronic pain.

In the context of the evaluation of a national variation procedure for Durogesic (fentanyl) on the risk of drug dependence, developing tolerance and drug abuse, the Netherlands requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the assessment from the Netherlands. Considering the evidence and the growing concerns regarding the increased consumption of prescription opioids in Europe, the PRAC supported the update of the product information of Durogesic (fentanyl)⁵² to include additional information on the development of tolerance in long-term use setting, as well as on the risk of opioid use disorder, including relevant risk factors.

⁵¹ Transdermal patch

⁵² Update of SmPC section 4.4. The package leaflet is to be updated accordingly

11.1.2. Paracetamol (NAP) - IE/H/0835/001/II/056/G, PA0678/037/001

Applicant(s): GSK Consumer Healthcare (Paracetamol + Pseudoephedrine 500mg/30 mg, Panadol with Caffeine 500mg/65 mg)

PRAC Lead: Rhea Fitzgerald

Scope: PRAC consultation on national variations on proposed amendments of the product information aimed at strengthening the risk minimisation measures for paracetamol regarding the risk of hepatotoxicity at therapeutic doses, on request of Ireland

Background

Paracetamol is an antipyretic and analgesic medicine indicated for the treatment of fever and pain.

In the context of the evaluation of a national variation procedure on the risk of hepatotoxicity at therapeutic doses, Ireland requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the assessment from Ireland. Considering that information on the risk of hepatotoxicity in patients taking paracetamol at doses within the therapeutic range is already reflected in the product information of paracetamol-containing medicinal products, the PRAC advised that no further updates of the product information are warranted. The PRAC emphasised the need for healthcare professionals to follow current risk minimisation measures and advised that communication on this risk is to be considered at national level to increase awareness.

11.2. Other requests

11.2.1. Bupropion (NAP) - NL/H/PSUFU/00000461/201812

Applicant(s): various

PRAC Lead: Liana Gross-Martirosyan

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure on increased sexual function with bupropion use including all available information including cases published in the literature, data from non-clinical studies, clinical and epidemiological studies and post marketing spontaneous, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure (PSUSA/00000461/201812) concluded in September 2019, on request of the Netherlands

Background

Bupropion is a selective inhibitor of the neuronal re-uptake of noradrenaline and dopamine indicated for the treatment of major depressive disorder (MDD) and for the treatment of nicotine dependence as an aid to smoking cessation.

Based on the assessment of the recent PSUR single assessment (PSUSA) procedure for bupropion (PSUSA/00000461/201812) concluded in September 2019, the PRAC considered that a review on increased sexual function with bupropion use should be further assessed. For further background, see [PRAC minutes September 2019](#).

On request of the CMDh, MAHs for bupropion-containing product(s) submitted the requested safety reviews for evaluation within a worksharing periodic safety update (PSU) follow-up procedure. In the context of the ongoing evaluation of the PSU FU procedure, the Netherlands, as lead Member State (LMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the conclusions by the LMS. Having considered all available data, the PRAC advised that there is insufficient evidence at present to support a causal association between administration of bupropion and increased sexual function. The PRAC agreed that no updates of product information were warranted at this stage, however increased sexual function should be further monitored in future PSURs.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

None

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

None

12.4. Cooperation within the EU regulatory network

12.4.1. EudraVigilance data analysis system (EVDAS) - training for National Competent Authorities (NCAs)

The EMA secretariat informed the PRAC of the training programme to be provided by the EMA on the EudraVigilance data analysis system (EVDAS) in 2020.

12.4.2. PRAC strategic review and learning meeting (SRLM) under the Croatian presidency of the European Union (EU) Council - Split, Croatia, 22-24 April 2020 - Agenda

PRAC lead: Nikica Mirošević Skvrce, Željana Margan Koletić

The Croatian delegation informed the PRAC of the postponement of the PRAC strategic review and learning meeting (SRLM) under the Croatian presidency of the European Union (EU) Council to be held jointly with CMDh from 22-24 April 2020 to 02-04 June 2020. The main agenda topics for the meeting were presented to the PRAC accordingly.

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

None

12.8. Planning and reporting

None

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

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

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the Granularity and Periodicity Advisory Group (GPAG) focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights.

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 March 2020, reflecting the PRAC's comments impacting on the data lock point (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 of March 2020, the updated EURD list was adopted by the CHMP and CMDh at their March 2020 meetings and published on the EMA website on 01/04/2020, see:

[Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

12.11. Signal management

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

PRAC lead: Menno van der Elst

None

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Additional monitoring – status of lenalidomide-containing product(s)

The PRAC was consulted on the additional monitoring (AM) status of lenalidomide-containing products, considering the inclusion of Revlimid and Lenalidomide Accord in the AM list and other nationally authorised lenalidomide-containing products which are not included in the AM list. Further discussion will be scheduled in June/July 2020.

12.12.2. 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 the EMA website on 25/03/2020, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

12.12.3. Management and reporting of adverse reactions to medicinal products

None

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.13.2. EudraVigilance – annual report 2019

At the organisational matters teleconference on 26 March 2020, the EMA secretariat

presented to the PRAC the highlights of the 2019 EudraVigilance annual report for the European Parliament, the Council and the Commission.

Post-meeting note: On 20 March 2020, the annual report was published on the EMA website ([EMA/640614/2019](https://www.ema.europa.eu/en/press-room/2020/03/2020-03-20-annual-report)).

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

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

None

12.14.3. Good pharmacovigilance practice (GVP) module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' – request for input on terminology

PRAC lead: Sabine Straus

In line with the [PRAC work plan 2020](#), and as a follow-up to the last discussion on the need to revise GVP module XVI on 'Risk minimisation measures: selection of tools and effectiveness indicators' (for further background, see [PRAC minutes October 2019](#)⁵³), at the organisational matters teleconference on 26 March 2020, the EMA secretariat presented to the PRAC -on behalf of the drafting group for the revision of GVP module XVI- an overview of PRAC members' responses regarding the terminology to be used in the revised module. PRAC members were invited to provide written comments by 10 April 2020. Further discussion will be scheduled in June/July 2020.

12.15. Post-authorisation safety studies (PASS)

12.15.1. EU post-authorisation safety studies (EU PAS) register - notification of imposed studies registered in the EU PASS Register to Member States

At the organisational matters teleconference on 26 March 2020, the EMA secretariat presented to the PRAC a proposal to cease the notification process of imposed studies registered in the European Union electronic register of post-authorisation studies (EU PAS Register) to Member States and to remove the related text in the addendum of GVP Module VIII on 'Post-authorisation safety studies'. The PRAC agreed with the proposal.

12.15.2. Post-authorisation Safety Studies – imposed PASS

None

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

None

⁵³ Held 30 September – 03 October 2019

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Drug-induced hepatotoxicity – draft PRAC guidance

PRAC lead: Menno van der Elst, Martin Huber

In line with the [PRAC work plan 2020](#), and as a follow-up to the last discussion (for further background, see [PRAC minutes October 2019](#)⁵⁴), the EMA

The drafting group presented to the PRAC the draft guidance for assessing drug-induced hepatotoxicity. PRAC members were invited to provide written comments by 07 April 2020. Follow-up discussion is planned in May 2020.

12.20.2. EMA new organisational structure for human medicines division

The Head of the EMA [Human Medicines Division](#) provided to the PRAC an overview of the new organisational structure of the division.

12.20.3. Medical Dictionary for Regulatory Activities (MedDRA) points to consider group – call for EU expert nomination

As a follow-up to the February 2020 discussion (for further background, see [PRAC minutes February 2020](#)), the PRAC nominated experts to the Medical Dictionary for Regulatory

⁵⁴ Held 30 September – 03 October 2019

Activities (MedDRA) points to consider group.

12.20.4. Serious cutaneous adverse reactions (SCARs) - PRAC guidance update

PRAC lead: Sabine Straus, Zane Neikena

At the organisational matters teleconference on 26 March 2020, the EMA secretariat on behalf of the drafting group presented to the PRAC the updated guidance for assessing serious cutaneous adverse reactions (SCARs). PRAC members were invited to provide written comments by 24 April 2020. Follow-up discussion is planned in May 2020.

13. Any other business

None

14. Annex I – Signals assessment and prioritisation⁵⁵

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria 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 timetables⁵⁶.

14.1.1. Apixaban – ELIQUIS (CAP)

Applicant(s): Bristol-Myers Squibb, Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Signal of erythema multiforme

EPITT 19534 – New signal

Lead Member State(s): NL

14.1.2. Dabigatran – PRADAXA (CAP)

Applicant(s): Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of gastro-oesophagitis

EPITT 19530 – New signal

Lead Member State(s): DK

⁵⁵ 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

⁵⁶ Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

14.1.3. Lamotrigine (NAP)

Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of photosensitivity

EPITT 19548 – New signal

Lead Member State(s): NL

14.2. New signals detected from other sources

None

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per 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. Apixaban - EMEA/H/C/005358

Scope: Prevention of venous thromboembolic events (VTE), prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE

15.1.2. Doxorubicin - EMEA/H/C/005320

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

15.1.3. Indacaterol, mometasone furoate - EMEA/H/C/005516

Scope: Treatment of asthma

15.1.4. Melphalan - EMEA/H/C/005173

Scope: Treatment of multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukaemia, childhood neuroblastoma, ovarian adenocarcinoma and mammary adenocarcinoma as well as conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (HSCT) in haematological diseases

15.1.5. Methylthioninium chloride - EMEA/H/C/002776

Scope: Aid for the enhanced visualisation and detection of colorectal lesions in adult patients undergoing screening/surveillance colonoscopy for colorectal cancer

15.1.6. Trastuzumab - EMEA/H/C/005209

Scope: Treatment of metastatic and early breast cancer and metastatic gastric cancer (MGC)

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

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. 5-aminolevulinic acid - AMELUZ (CAP) - EMEA/H/C/002204/II/0040

Applicant: Biofrontera Bioscience GmbH

PRAC Rapporteur: Martin Huber

Scope: Submission of an updated RMP (version 11.1) brought in line with revision 2 of GVP module V on 'Risk management systems', including also the implementation of changes as requested by PRAC in the conclusions of the periodic safety update report single assessment (PSUSA) procedure PSUSA/00010006/201806 adopted in February 2019

15.2.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0033, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Submission of an updated RMP (version 11) in line with revision 2 of GVP module V on 'Risk management systems'. The protocol for study 20150136 (listed as a category 1 in the RMP/Annex II): an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices is updated and the enrolment period extended by 1 year. As a consequence, the milestones in the RMP are updated accordingly. In addition, the RMP includes a proposed update to the milestone of study 20180138 (listed as a category 3 study in the RMP): long-term follow-up of patients enrolled in TOWER study (a phase 3, randomized, open label study investigating the efficacy of the bispecific T-cell engager (BiTE) antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL))

15.2.3. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/II/0015, Orphan

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of an updated RMP (version 9.0) in order to remove as missing information drug-drug interaction, use in adolescents, adults and elderly, use in patients with an ethnic origin other than Caucasian, use in patients with hepatic and renal

impairment as well as potential harm from overdose

15.2.4. Follitropin alfa - GONAL-F (CAP) - EMEA/H/C/000071/II/0147

Applicant: Merck Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Submission of an updated RMP (version 2.1) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template), to remove the important identified risks of 'ovarian hyperstimulation syndrome (OHSS)', 'thromboembolic events usually with OHSS', 'hypersensitivity reactions, including anaphylactic reactions', 'asthma aggravated/exacerbation', 'multiple pregnancies' and 'gynecomastia in males'. In addition, the RMP is updated to remove the important potential risks of 'breast cancer', 'other reproductive system cancers', 'ectopic pregnancy' and 'congenital abnormalities'. Finally, the RMP is updated to increase the age from 40 to 42 years for the missing information of 'women older than 40 years'

15.2.5. Follitropin alfa, lutropin alfa - PERGOVERIS (CAP) - EMEA/H/C/000714/II/0066

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 5.3) in order to bring it in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template), to remove the important identified risks of 'ovarian hyperstimulation syndrome (OHSS)', 'thromboembolic events usually with OHSS' and 'hypersensitivity reactions', to remove the important potential risks of 'breast cancer', 'ovarian cancer', 'endometrial cancer', 'congenital anomalies' and 'malignant melanoma'

15.2.6. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/II/0081

Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of an updated RMP (version 6.0) in order to update the safety specifications based on a review of the preclinical, clinical, post-marketing and literature data. In addition, the MAH took the opportunity to update the RMP in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.2.7. Lonoctocog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/II/0030

Applicant: CSL Behring GmbH

PRAC Rapporteur: Sonja Hrabcik

Scope: Submission of an updated RMP (version 5.0) to introduce information on ongoing study CSL627_3001: a phase 3 open label, multicentre, extension study to assess the safety and efficacy of recombinant coagulation factor VIII (rVIII-single-chain CSL627 (lonoctocog alfa)) in subjects with severe haemophilia A. The RMP is also amended to reflect updated information on registries/non-interventional study (NIS) to demonstrate how previously untreated patient (PUP) clinical data will be complemented following the

stop of enrolment of arm 2 of study CSL627 3001. The registries (e.g. addition of registry American Thrombosis and Hemostasis Network [ATHN] 8, removal of registries ATHN 2 and Dutch haemophilia registry) considered as additional pharmacovigilance activities have been updated respectively

15.2.8. [Lopinavir, ritonavir - ALUVIA \(Art 58⁵⁷\) - EMEA/H/W/000764/WS1711/0112;KALETRA \(CAP\) - EMEA/H/C/000368/WS1711/0181](#)

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.0) in order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to review the safety information contained in the RMP, removed an important potential risk of drug interaction with telaprevir and boceprevir (hepatitis C virus (HCV) protease inhibitors) and missing information regarding use of lopinavir/ritonavir (LPV/r) in elderly patients

15.2.9. [Ponatinib - ICLUSIG \(CAP\) - EMEA/H/C/002695/II/0053, Orphan](#)

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Annika Folin

Scope: Submission of an updated RMP (version 20) in order to remove study AP24534-14-401: a post-marketing observational registry to evaluate the incidence of and risk factors for vascular occlusive events associated with Iclusig (ponatinib) in routine clinical practice in the US (OMNI) from the pharmacovigilance plan. In addition, the MAH took the opportunity to remove the distribution of the educational material in line with the conclusions of variation II/51 adopted in September 2019

15.2.10. [Telotristat ethyl - XERMELO \(CAP\) - EMEA/H/C/003937/II/0021, Orphan](#)

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of an updated RMP (version 5.0) in order to bring it in line with revision 2 of GVP module V on 'Risk management systems'

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

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).

⁵⁷ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

15.3.1. [Anakinra - KINERET \(CAP\) - EMEA/H/C/000363/II/0070](#)

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Extension of indication to include the treatment of familial Mediterranean fever (FMF) to be given in combination with colchicine, if appropriate. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 5.2) are updated accordingly. In addition, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.2. [Atezolizumab - TECENTRIQ \(CAP\) - EMEA/H/C/004143/II/0033](#)

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express programmed death-ligand 1 (PD-L1) based on the results of pivotal study GO29431 (IMpower110): a phase 3, open label, randomized study of atezolizumab compared with a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1-selected, chemotherapy-naïve patients with stage IV non-squamous or squamous NSCLC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 12.0) are updated accordingly

15.3.3. [Autologous CD34⁺ enriched cell fraction that contains CD34⁺ cells transduced with retroviral vector that encodes for the human ANA cDNA sequence - STRIMVELIS \(CAP\) - EMEA/H/C/003854/II/0024, Orphan](#)

Applicant: Orchard Therapeutics (Netherlands) BV, ATMP⁵⁸

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information following the completion of study STRIM-004 (listed as a category 3 study in the RMP): a non-interventional long term follow up of the subjects including paediatric patients who received Strimvelis gene therapy. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor administrative changes in the product information

15.3.4. [Baricitinib - OLUMIANT \(CAP\) - EMEA/H/C/004085/II/0016](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Extension of indication to include a new indication in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 8.1) are updated accordingly. In addition, the MAH

⁵⁸ Advanced therapy medicinal product

took the opportunity to update the list of local representatives in the package leaflet and to introduce minor editorial changes to the labelling. Furthermore, Annex II is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.5. Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0008/G

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (172 µg / 5 µg / 9 µg); 2) update of sections 4.1, 4.2, 4.4, 5.1 and 5.2 to extend the indication to the maintenance treatment in adult patients with asthma who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or who are already treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist plus a long-acting muscarinic antagonist. The RMP (version 6.1) is updated in accordance

15.3.6. Bortezomib - BORTEZOMIB FRESENIUS KABI (CAP) - EMEA/H/C/005074/II/0001/G

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Grouped variations consisting of: 1) addition of a new pack size for the solution for injection, with a fill volume for a single dose vial of 1 mg per vial in addition to the authorised 3.5 mg per vial; 2) addition of a new pack size for the powder for solution for injection with a fill volume for a single dose vial of 2.5 mg per vial in addition to the authorised 3.5 mg per vial. The RMP (version 2.0) is updated accordingly

15.3.7. Budesonide - JORVEZA (CAP) - EMEA/H/C/004655/X/0007/G, Orphan

Applicant: Dr. Falk Pharma GmbH

PRAC Rapporteur: Zane Neikena

Scope: Grouped application consisting of: 1) extension application to add a new strength of 0.5 mg for budesonide orodispersible tablets; 2) extension of indication to include the maintenance of remission for the 0.5 mg and 1 mg orodispersible tablets. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect the recommended daily dose and duration of treatment of Jorveza (budesonide) for the maintenance of remission, to update the list of adverse reactions and the clinical efficacy and safety information based on the results of study BUL-2/EER: a double-blind, randomized, placebo-controlled, phase 3 study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis. The package leaflet is updated accordingly. In addition, the RMP (version 2.1) is updated accordingly and is brought in line with revision 2 of the guidance on the format of RMP in the EU (template). The MAH also took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1); 3) addition of a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza (budesonide) 1 mg orodispersible tablet

15.3.8. Ceftazidime, avibactam - ZAVICEFTA (CAP) - EMEA/H/C/004027/II/0015

Applicant: Pfizer Ireland Pharmaceuticals

PRAC Rapporteur: Rugile Pilviniene

Scope: Extension of indication to include paediatric patients aged 3 months to less than 18 years for Zavicefta (ceftazidime/avibactam) based on data from three paediatric studies namely, study D4280C00014: a phase 1 study to assess the pharmacokinetics, safety and tolerability of a single dose of ceftazidime-avibactam (CAZ-AVI) in children from 3 months of age to <18 years who are receiving systemic antibiotic therapy for suspected or confirmed infection; study C3591004: a single blind, randomised, multicentre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of ceftazidime and avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs); and study C3591005: a single blind, randomised, multicentre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam compared with cefepime in children from 3 months to less than 18 years of age with complicated urinary tract infections (CUTIs); as well as population PK modelling/simulation analyses (CAZ-MS-PED-01 and CAZ-MS-PED-02). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.3 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 3.0) are updated accordingly. In addition, the MAH took the opportunity to correct sections 2 and 4.4 of the SmPC and the package leaflet with information on sodium content, as well as section 5.2 of the SmPC with information on volumes of distribution of ceftazidime and avibactam. Furthermore, the MAH also introduced minor correction in the Czech product information

15.3.9. Conestat alfa - RUCONEST (CAP) - EMEA/H/C/001223/II/0053/G

Applicant: Pharming Group N.V

PRAC Rapporteur: Jan Neuhauser

Scope: Grouped variations consisting of an extension of indication to include children in the treatment of acute angioedema attacks with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency, based on the results from study C1 1209: an open-label, phase 2, single arm study to evaluate the safety, immunogenicity, pharmacokinetics and efficacy of recombinant human C1 inhibitor for the treatment of acute attacks in paediatric patients with hereditary angioedema, from 2 up to and including 13 years of age. In addition, final efficacy and safety data from the open label extension (OLE) phases of 1) study C1 1304: a randomised, placebo-controlled, double-blind, multicentre study performed in order to demonstrate the efficacy of recombinant human C1 inhibitor (rhC1INH) at 100 U/kg in patients with HAE with attacks of angioedema; 2) study C1 1205: a randomised, placebo-controlled, double-blind phase 2 study on the safety and efficacy of rhC1INH at doses of 50 and 100U/kg in relieving eligible attacks of angioedema with involvement of sub-mucosal tissues in patients with HAE; and completed study C1 1310: a phase 3, randomized, placebo-controlled trial on rhC1INH relieved symptoms of hereditary angioedema attacks; together with the final results of studies C1 1207 and 3201 concerning prophylactic treatment of HAE patients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1, 5.2 and 5.3 are updated. The package leaflet and the RMP (version 19.0) are updated accordingly. The RMP is also brought in line with revision 2.0.1 of the guidance on

the format of RMP in the EU (template). Furthermore, the MAH requested an extension for the completion of registry study C1 1412: C1 inhibitor treatment registry to assess the safety and immunological profile of Ruconest (conestat alfa) in the treatment of HAE attacks, from March 2020 to June 2022. Finally, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.10. Desloratadine - DESLORATADINE RATIOPHARM (CAP) - EMEA/H/C/002404/II/0023/G

Applicant: ratiopharm GmbH

PRAC Rapporteur: Laurence de Fays

Scope: Grouped variations consisting of: 1) change in the legal status of Desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Desloratadine ratiopharm and the post-marketing experience already available with other medicinal products containing similar long acting histamine antagonists. The RMP (version 1.0) is updated accordingly. In addition, the MAH also took the opportunity to bring the product information (PI) in line with the latest quality review of documents (QRD) template (version 10.1), to update the list of local representatives in the package leaflet and to introduce editorial changes.; 2) deletion of the therapeutic indication in adolescents aged 12 years and older for the relief of symptoms associated with allergic rhinitis and urticaria. As a consequence, section 4.1 of the SmPC is updated. The package leaflet is updated accordingly

15.3.11. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/X/0045

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Extension application to introduce two new strengths of 3 mg and 4.5 mg solution for injection. The RMP (version 4.1) is updated accordingly

15.3.12. Etravirine - INTELENCE (CAP) - EMEA/H/C/000900/II/0058

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Extension of indication in order to include patient population from 2 to 6 years of age based on the 48 week study results from study TMC125-C234/P1090: a phase 1/2, open-label trial to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of etravirine (ETR) in antiretroviral (ARV) treatment-experienced human immunodeficiency virus-1 (HIV-1) infected infants and children, aged ≥ 2 months to < 6 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 13.1) are updated accordingly. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems' and revision 2.0.1 of the guidance on the format of RMP in the EU (template) leading to a reclassification of safety concerns. Finally, the MAH took the opportunity to introduce minor updates to the product information

15.3.13. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0020

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC to include anaphylactic reactions as an adverse drug reaction. The package leaflet and the RMP (version 5.2) are updated accordingly

15.3.14. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) - CERVARIX (CAP) - EMEA/H/C/000721/II/0106

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.4 and 5.1 of the SmPC based on final results from study HPV-019 (listed as a category 3 study in the RMP) (in fulfilment of MEA 080): a safety and immunogenicity study of Cervarix (human papillomavirus vaccine) in human immunodeficiency virus (HIV)-positive female subjects aged 15-25 years as compared to human papillomavirus 4 (HPV-4). In addition, the MAH took the opportunity to reflect an update in section 4.2 of the SmPC to indicate that limited clinical data is now available in 4-6 years old children based on study HPV-073: a safety and immunogenicity study of Cervarix (human papillomavirus vaccine) in girls aged 4-6 years, as an alternative to the current adolescent HPV vaccination schedule. The RMP (version 21.0) is updated accordingly and also reflect the removal of the use of Cervarix (human papillomavirus vaccine) in HIV-infected subjects or subjects with known immune deficiencies as missing information. Furthermore, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.15. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0018/G

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Ilaria Baldelli

Scope: Grouped variations consisting of: 1) introduction of a new container closure system: Pumpcart cartridge to be used with insulin infusion pump systems (EU/1/16/1160/012); 2) introduction of a new multipack presentation of Fiasp (insulin aspart) 100 units/mL PumpCart solution for injection in cartridge (EU/1/16/1160/013). The RMP (version 4.0) is updated accordingly

15.3.16. Iron - VELPHORO (CAP) - EMEA/H/C/002705/II/0021

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of section 5.1 of the SmPC in order to add information related to the results of the VERIFIE study (listed as a category 3 study in the RMP): a non-interventional voluntary PASS trial to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro (iron) in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis. Furthermore, minor editorial changes in section 4.2 of

the SmPC were introduced to provide consistent information between the SmPC, the labelling and the package leaflet. The RMP (version 8.0) is updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.17. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0083/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) extension application to add a new strength of 75 mg film-coated tablets of ivacaftor to enable administration to patients aged 6 to less than 11 years; 2) update of sections 4.1, 4.2 and 6.5 the SmPC for the 150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 11 years old in combination with tezacaftor/ivacaftor and to bring it in line with the new dosage form. The package leaflet and the RMP (version 8.6) are updated in accordance. In addition, the MAH took the opportunity to implement minor updates throughout the product information

15.3.18. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0019/G, Orphan

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Grouped variations consisting of: 1) submission of the final report from study NSMM-5001 (listed as a specific obligation (SOB) in Annex II-E on 'Specific obligation to complete post-authorisation measures for the conditional marketing authorisation): a global, prospective, non-interventional, observational efficacy study in multiple myeloma patients. Annex II and the RMP (version 5) are updated accordingly; 2) submission of an updated RMP (version 5) in order to extend the due date of post-authorisation efficacy study (PAES) C16010 (listed in Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product': provision of an interim report of overall survival (OS) at the time of the third interim analysis and provision of a final report for the final analysis of OS from the phase 3, randomized, double-blind study C16010 in adult patients with relapsed and/or refractory multiple myeloma. The MAH took the opportunity to correct a typographical error in Annex II

15.3.19. Ixekizumab - TALTZ (CAP) - EMEA/H/C/003943/II/0030

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with active axial spondyloarthritis. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 10.1) are updated accordingly. The product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.20. Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/X/0007

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension application to introduce a new pharmaceutical form (solution for infusion), a new strength (10mg/ml) and a new route of administration (intravenous use). The RMP (version 1.0) is updated accordingly

15.3.21. Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/II/0030

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Change in the legal status from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Fortacin (lidocaine/prilocaine), the post-marketing experience already available with other medicinal products containing amide local anaesthetics and in view of making the medicinal product more accessible to the target population. The RMP (version 3.1) is updated accordingly. Furthermore, the product information is also brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.22. Lurasidone - LATUDA (CAP) - EMEA/H/C/002713/II/0029

Applicant: Aziende Chimiche Riunite Angelini Francesco S.p.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to add the treatment of schizophrenia in adolescent from 13 to less than 18 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 8.0) are updated accordingly. In addition, the MAH took the opportunity to update the product information in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and to update the list of local representatives in the package leaflet

15.3.23. Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/II/0023

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and immunogenicity information based on final results from study B1971033 (listed as a category 3 study in the RMP) (in fulfilment of MEA 007): a duration of immunity study to assess persistence of hSBA (serum bactericidal activity using human complement) response for up to 48 months after completion of vaccination with Trumenba (meningococcal group B vaccine) and the immunogenicity, safety, and tolerability of a booster dose of Trumenba (meningococcal group B vaccine). The RMP (version 3) is updated accordingly and includes changes agreed in variation II/13 as well as editorial changes. In addition, the MAH took the opportunity to introduce editorial changes in Annex II, in the labelling and in the package leaflet

15.3.24. Meningococcal group B vaccine (recombinant, component, adsorbed) - BEXSERO (CAP) - EMEA/H/C/002333/II/0088

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2 and 5.1 of the SmPC in order to reflect the final results from study V72_38OB (listed as category 3 study in the RMP): an observational effectiveness study of the impact of Bexsero (meningococcal group B vaccine) vaccination. The package leaflet and the RMP (version 7.3) are updated accordingly. In addition, the MAH took the opportunity to introduce some rewording in section 5.1 of the SmPC, to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to amend minor typos detected in the European annexes

15.3.25. Nintedanib - OFEV (CAP) - EMEA/H/C/003821/II/0027, Orphan

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of indication to include the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype based on the results of pharmacology studies and the double-blind, randomised, placebo-controlled phase 3 trial (INBUILD). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 9.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes in the product information. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.26. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/II/0050

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Update of sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, as requested in the conclusions of LEG 014 finalised in March 2019. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Netherlands and Portugal in the package leaflet

15.3.27. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0035

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO⁵⁹ stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line

⁵⁹ International Federation of Gynaecology and Obstetrics

platinum-based chemotherapy with bevacizumab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The package leaflet and the RMP (version 19.0) are updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on updated safety data analysis. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.28. Olaparib - LYNPARZA (CAP) - EMEA/H/C/003726/II/0036

Applicant: AstraZeneca AB

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include the use of Lynparza (olaparib) tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The package leaflet and the RMP (version 20) are updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza (olaparib) hard capsules are revised based on updated safety data analysis

15.3.29. Pneumococcal polysaccharide conjugate vaccine (adsorbed) - SYNFLORIX (CAP) - EMEA/H/C/000973/II/0146

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from a hospital-based surveillance study assessing the impact of Synflorix (pneumococcal polysaccharide conjugate vaccine) immunisation programme in Kenya on pneumonia, invasive pneumococcal disease (IPD) and replacement disease (in fulfilment of post-authorisation measure MEA 021.8). The RMP (version 18) is updated accordingly. In addition, the RMP is updated in line with revision 2 of GVP module V on 'Risk management systems'

15.3.30. Ramucirumab - CYRAMZA (CAP) - EMEA/H/C/002829/II/0038

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add posterior reversible encephalopathy syndrome (PRES) and dysphonia as a warning and as an undesirable effect respectively. The labelling, package leaflet and the RMP (version 9.3) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.31. Ravulizumab - ULTOMIRIS (CAP) - EMEA/H/C/004954/II/0002

Applicant: Alexion Europe SAS

PRAC Rapporteur: Kimmo Jaakkola

Scope: Extension of indication to include the treatment of patients with atypical haemolytic uremic syndrome (aHUS). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The package leaflet and the RMP (version 1.6) are updated accordingly. In addition, Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated to include in the educational materials the risk of thrombotic microangiopathy (TMA) with the new indication

15.3.32. Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1724/0029; RITEMVIA (CAP) - EMEA/H/C/004725/WS1724/0029; TRUXIMA (CAP) - EMEA/H/C/004112/WS1724/0032

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study CT-P10 3.3 (listed as a category 3 study in the RMP): a phase 3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics (PK) and non-inferiority of efficacy for CT-P10 (biosimilar rituximab) in comparison with Rituxan (rituximab), each administered in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with advanced follicular lymphoma. The RMP (version 9.1) is updated accordingly and aligned with the safety concerns of MabThera (rituximab)

15.3.33. Ruxolitinib - JAKAVI (CAP) - EMEA/H/C/002464/II/0044

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of the SmPC sections 5.1 and 4.8 with efficacy and safety information to reflect the 5-year follow-up data from the final clinical study report (CSR) of study B2301 week 256 (as an imposed study in Annex II-D 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'): a phase 3, open-label, randomised, controlled study comparing the efficacy and safety of the JAK inhibitor ruxolitinib to best available therapy (BAT) in adult patients with polycythemia vera (PV) who were resistant to or intolerant of hydroxyurea. The RMP (version 11) is updated accordingly (assessed with variation II/43)

15.3.34. Sebelipase alfa - KANUMA (CAP) - EMEA/H/C/004004/II/0026/G, Orphan

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the clinical information based on the pooled safety and efficacy analysis of already submitted studies (namely study LAL-CL04: an open label multicentre extension study to evaluate the long-term safety, tolerability, and efficacy of sebelipase alfa (SBC-102) in adult subjects with liver dysfunction due to lysosomal acid lipase deficiency (LAL-D) who previously received treatment in study LAL-CL01; study LAL-CL03: an open label, multicentre, dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to LAL-D; study LAL-CL06: a multicentre, open-label study of sebelipase alfa in patients with

LAL-D; study LAL-CL08: a phase 2, open label, multicentre study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sebelipase alfa in infants with rapidly progressive LAL-D; study LAL-CL02: a multicentre, randomized, placebo-controlled study of SBC-102 in patients with LAL-D) and updated population pharmacokinetic (PK) analyses in children and adults. The package leaflet and the RMP (version 4.0) are updated accordingly. Annex II is also updated to remove the obligation related to the provision of study LAL-CL08; 2) submission of the final report from study LAL-EA01: an open-label study with sebelipase alfa 1 mg/kg every other week for up to 78 weeks or until drug commercialisation in the United States (US) patients who did not otherwise qualify for an active sebelipase alfa trial (expanded access protocol)

15.3.35. Secukinumab - COSENTYX (CAP) - EMEA/H/C/003729/II/0053/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of non-radiographic axial spondyloarthritis (nr-axSpA)/axial spondyloarthritis (axSpA) without radiographic evidence. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 of the SmPC are amended. The package leaflet and the RMP (version 5.0) are updated accordingly; 2) change in the due date of the psoriasis registry (listed as a category 3 study in the RMP)

15.3.36. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/II/0024

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: Submission of the final report of study CLDE225X2116 (listed as a category 3 study in the RMP): an interventional phase 1b/2, open-label, multicentre, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 (sonidegib) and INC424 (ruxolitinib) in subjects with myelofibrosis. The RMP (version 7.1) is updated accordingly

15.3.37. Talazoparib - TALZENNA (CAP) - EMEA/H/C/004674/II/0001

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations in patients with severe renal impairment and update pharmacokinetic (PK) information based on the results from PK study MDV3800-01 (C3441001) (listed as a category 3 study in the RMP): a phase 1 open-label pharmacokinetics and safety study of talazoparib (MDV3800) in patients with advanced solid tumours and normal or varying degrees of renal impairment. The RMP (version 1.0) is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes throughout the product information and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

15.3.38. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/X/0015/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Grouped variations consisting of: 1) extension application to add a new strength of 50/75mg film-coated tablets of tezacaftor/ivacaftor to enable administration to patients aged 6 to less than 11 years; 2) update of sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.1 of the SmPC for the 100/150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 11 years old in combination with ivacaftor and to bring it in line with the new dosage form. The package leaflet and the RMP (version 2.1) are updated in accordance. In addition, the MAH took the opportunity to implement minor updates in the product information

15.3.39. Thiotepa - TEPADINA (CAP) - EMEA/H/C/001046/X/0036, Orphan

Applicant: Adienne S.r.l.

PRAC Rapporteur: Ghania Chamouni

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (400 mg powder and solvent for solution for infusion). The RMP (version 14) is updated accordingly

15.3.40. Trastuzumab - OGIVRI (CAP) - EMEA/H/C/004916/II/0009

Applicant: Mylan S.A.S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final clinical study report for study MYL-Her-3001: a multicentre, double-blind, randomized, parallel-group, phase 3 study of the efficacy and safety of Hercules (trastuzumab Mylan S.A.S) plus taxane versus Herceptin (trastuzumab) plus taxane as first line therapy in patients with epidermal growth factor receptor 2+ (HER2+) metastatic breast cancer) with the final overall survival (OS). The RMP (version 3) is updated accordingly

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

16.1.1. Agalsidase beta - FABRAZYME (CAP) - PSUSA/00000070/201907

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

16.1.2. Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (Δ LNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) - ZALMOXIS⁶⁰ - PSUSA/00010530/201908

Applicant: MolMed S.p.A, ATMP⁶¹

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.3. Asenapine - SYCREST (CAP) - PSUSA/00000256/201908

Applicant: N.V. Organon

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.4. Baricitinib - OLUMIANT (CAP) - PSUSA/00010578/201908

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.5. Burosumab - CRYSVITA (CAP) - PSUSA/00010669/201908

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.6. Caplacizumab - CABLIVI (CAP) - PSUSA/00010713/201908

Applicant: Ablynx NV

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

⁶⁰ European Commission (EC) marketing authorisation withdrawal dated 09 October 2019

⁶¹ Advanced therapy medicinal product

16.1.7. Chlormethine - LEDAGA (CAP) - PSUSA/00010587/201908

Applicant: Helsinn Birex Pharmaceuticals Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.1.8. Cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil - STRIBILD (CAP) - PSUSA/00010082/201908

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.9. Cobimetinib - COTELLIC (CAP) - PSUSA/00010450/201908

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.10. Copper (⁶⁴Cu) chloride - CUPRYMINA (CAP) - PSUSA/00010040/201908

Applicant: A.C.O.M. - Advanced Center Oncology

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.11. Dabrafenib - TAFINLAR (CAP) - PSUSA/00010084/201908

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.12. Damoctocog alfa pegol - JIVI (CAP) - PSUSA/00010732/201908

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.13. Doravirine - PIFELTRO (CAP) - PSUSA/00010729/201908

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.14. Doravirine, lamivudine, tenofovir disoproxil - DELSTRIGO (CAP) - PSUSA/00010731/201908

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.15. Eliglustat - CERDELGA (CAP) - PSUSA/00010351/201908

Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.16. Eravacycline - XERAVA (CAP) - PSUSA/00010718/201908

Applicant: Tetrphase Pharmaceuticals Ireland Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.17. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - PSUSA/00010352/201908

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁶²

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.18. Ferric maltol - FERACCRU (CAP) - PSUSA/00010476/201908

Applicant: Norgine B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Human alpha₁-proteinase inhibitor⁶³ - RESPREEZA (CAP) - PSUSA/00010410/201908

Applicant: CSL Behring GmbH

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

⁶² Advanced therapy medicinal product

⁶³ Centrally authorised product(s) only

16.1.20. Hydrocortisone⁶⁴ - ALKINDI (CAP) - PSUSA/00010674/201908

Applicant: Diurnal Europe BV

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.21. Influenza vaccine (intranasal, live attenuated) - FLUENZ TETRA (CAP) - PSUSA/00001742/201908

Applicant: AstraZeneca AB

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.1.22. Lanadelumab - TAKHZYRO (CAP) - PSUSA/00010743/201908

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.23. Mecasermin - INCRELEX (CAP) - PSUSA/00001942/201908

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

16.1.24. Meropenem, vaborbactam - VABOREM (CAP) - PSUSA/00010727/201908

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.25. Nonacog alfa - BENEFIX (CAP) - PSUSA/00002183/201908

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.26. Pandemic influenza vaccine (H5N1) (whole virion, Vero cell derived, inactivated) - PANDEMIC INFLUENZA VACCINE H5N1 BAXTER (CAP); prepandemic influenza vaccine (H5N1) (whole virion, Vero cell derived, inactivated) - VEPACEL (CAP) - PSUSA/00002282/201908

Applicant: Ology Bioservices Ireland Limited

⁶⁴ Centrally authorised product(s) only, indicated for adrenal insufficiency, paediatric use only

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.27. Peginterferon alfa-2b - PEGINTRON (CAP); VIRAFERONPEG (CAP) - PSUSA/00002327/201907

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.28. Pyronaridine, artesunate - PYRAMAX (Art 58⁶⁵) - EMEA/H/W/002319/PSUV/0021

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUR procedure

16.1.29. Rolapitant - VARUBY (CAP) - PSUSA/00010592/201908

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.30. Ropeginterferon alfa-2b - BESREMI (CAP) - PSUSA/00010756/201908

Applicant: AOP Orphan Pharmaceuticals AG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.1.31. Sebelipase alfa - KANUMA (CAP) - PSUSA/00010422/201908

Applicant: Alexion Europe SAS

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Telotristat - XERMELO (CAP) - PSUSA/00010639/201908

Applicant: Ipsen Pharma

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

⁶⁵ Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

16.1.33. Tezacaftor, ivacaftor - SYMKEVI (CAP) - PSUSA/00010730/201908

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

16.1.34. Tisagenlecleucel - KYMRIAHA (CAP) - PSUSA/00010702/201908

Applicant: Novartis Europharm Limited, ATMP⁶⁶

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.35. Tivozanib - FOTIVDA (CAP) - PSUSA/00010636/201908

Applicant: EUSA Pharma (Netherlands) B.V.

PRAC Rapporteur: Rugile Pilviniene

Scope: Evaluation of a PSUSA procedure

16.1.36. Vemurafenib - ZELBORAF (CAP) - PSUSA/00009329/201908

Applicant: Roche Registration GmbH

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

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

16.2.1. Palonosetron - ALOXI (CAP); NAP - PSUSA/00002268/201907

Applicant(s): Helsinn Birex Pharmaceuticals Limited (Aloxi), various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Beclometasone, formoterol⁶⁷ (NAP) - PSUSA/00010068/201907

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

⁶⁶ Advanced therapy medicinal product

⁶⁷ For inhalation use only

16.3.2. Fosfomycin⁶⁸ (NAP) - PSUSA/00010336/201907

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.3. Fosfomycin⁶⁹ (NAP) - PSUSA/00010326/201907

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.4. Human coagulation factor IX (NAP) - PSUSA/00001617/201907

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.5. Meloxicam (NAP) - PSUSA/00010474/201907

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.6. Phleum pratense^{70 71 72} (NAP) - PSUSA/00010475/201907

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.7. Poliovirus type 1, poliovirus type 3 (oral, live, attenuated) vaccine (NAP) - PSUSA/00010642/201907

Applicant(s): various

PRAC Lead: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

16.3.8. Zaleplon (NAP) - PSUSA/00003140/201907

Applicant(s): various

⁶⁸ Intravenous (IV) formulation only

⁶⁹ Oral formulation only

⁷⁰ Allergen for therapy

⁷¹ For oromucosal use only

⁷² Medicinal product(s) authorised via mutually recognition procedure only

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

None

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, 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)⁷³

17.1.1. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSA/S/0049

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Amendment to a protocol previously agreed in July 2018 (PSP/S/0057.1) for a cerebrotendinous xanthomatosis registry: a long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic acid Leadiant (chenodeoxycholic acid)

17.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/PSA/S/0048

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Amendment to a protocol previously agreed in September 2017 (PSA/S/0021): a prospective, observational, non-interventional, post-marketing, patient registry to collect data on routine clinical care in patients treated with Kolbam (cholic acid)

17.1.3. Valproate (NAP) - EMEA/H/N/PSP/J/0074.2

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

PRAC Rapporteur: Jean-Michel Dogné

Scope: MAH's response to PSP/J/0074.1 [protocol for an observational study to evaluate and identify the best practices for switching of valproate in clinical practice, as required in the outcome of the referral procedure under Article 31 of Directive 2001/83/EC on valproate-containing products completed in February 2018 (EMEA/H/A-31/1454)] as per the request for supplementary information (RSI) adopted in November 2019⁷⁴

⁷³ In accordance with Article 107n of Directive 2001/83/EC

⁷⁴ Meeting held 28-31 October 2019

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁷⁵

17.2.1. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.9

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Amendment to a previously agreed protocol in August 2012 (FUM 075) for study P11-282 (Humira Adult Ulcerative Colitis Registry): a long-term non-interventional registry to assess safety and effectiveness of Humira (adalimumab) in patients with moderately to severely active ulcerative colitis (UC)

17.2.2. Botulinum toxin type A - NUCEIVA (CAP) - EMEA/H/C/004587/MEA 002

Applicant: Evolus Pharma Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Protocol (version 1.0) for study EV-010: a non-interventional post-authorisation safety study of Nuceiva (botulinum toxin type A) for the treatment of moderate-to-severe glabellar lines

17.2.3. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 002.1

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 002 [protocol for observational cohort study TV48125-MH-50037: a pregnancy registry assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab)] as per the request for supplementary information (RSI) adopted in September 2019

17.2.4. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 003.1

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: MAH's response to MEA 003 [protocol for observational cohort study TV48125-MH-50038: a pregnancy database study assessing pregnancy outcomes in patients treated with Ajovy (fremanezumab)] as per the request for supplementary information (RSI) adopted in September 2019

17.2.5. Fremanezumab - AJOVY (CAP) - EMEA/H/C/004833/MEA 005

Applicant: Teva GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Protocol for study TV48125-MH-50039: a long-term, prospective, phase 4,

⁷⁵ 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

observational study to evaluate the safety, including cardiovascular safety, of fremanezumab in patients with migraine in routine clinical practice

17.2.6. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 009

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Protocol for study EPI-ZOSTER-030 VS (targeted safety study): a non-interventional/observational prospective cohort study to evaluate the safety of Shingrix (herpes zoster vaccine) in older adults (≥ 50 year of age) in the United States [final clinical study report (CSR) expected in March 2025] (from initial opinion/marketing authorisation)

17.2.7. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - EMEA/H/C/004336/MEA 020

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Protocol for study EPI-ZOSTER-032 VS: a non-interventional/observational targeted safety study to evaluate the safety of Shingrix (herpes zoster vaccine) in the Medicare population (65 years old or older) in the United States [final clinical study report (CSR) expected in June 2027]

17.2.8. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 020

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Protocol for study CT-P13 4.8: an observational, prospective cohort study to evaluate the safety of Remsima (infliximab) subcutaneous in patients with rheumatoid arthritis (RA)

17.2.9. Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/MEA 036.2

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Amendment to protocol previously agreed in November 2018 for study CA184557: extension of the Dutch melanoma treatment registry (DMTR) to include paediatric subjects and collect safety data to obtain additional safety information in paediatric patients, as per the conclusion of variation II/64 concluded in October 2019 to add an additional milestone

17.2.10. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 003

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study 165-501: a multicentre, prospective global observational study to

evaluate the long term safety of subcutaneous injections of pegvaliase in patients with phenylketonuria [final clinical study report (CSR) expected in Q2 2030] (from opinion/initial marketing authorisation)

17.2.11. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 004

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study 165-503: a multicentre, prospective, longitudinal, observational study evaluating immunologic, inflammatory and laboratory parameters associated with long term Palynziq (pegvaliase) treatment in patients with phenylketonuria (PKU) in the United States [final clinical study report (CSR) expected in Q2 2030] (from opinion/initial marketing authorisation)

17.2.12. Pegvaliase - PALYNZIQ (CAP) - EMEA/H/C/004744/MEA 005

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Protocol for study 165-504: a prospective global multicentre observational safety surveillance study to assess maternal, foetal and infant outcomes of exposure to Palynziq (pegvaliase) during pregnancy and breastfeeding [final clinical study report (CSR) expected in Q2 2030] (from opinion/initial marketing authorisation)

17.2.13. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.6

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study C38072-AS-50027 (listed as category 3 study in the RMP): a long-term non-interventional study comparing the potential risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data

17.2.14. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 001.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

EMA resources: PM: Nuria Semis-Costa ; RMS: Nuria Semis-Costa; EPL: Catherine Draï

Scope: MAH's response to MEA 001 [protocol for study P19-633: a post-marketing registry-based prospective cohort study of long-term safety of risankizumab in real world setting in Denmark and Sweden [final study report due in December 2031]] as per the request for supplementary information (RSI) adopted in November 2019

17.2.15. Risankizumab - SKYRIZI (CAP) - EMEA/H/C/004759/MEA 002.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 002 [protocol for study P16-751 on pregnancy exposures and outcomes in psoriasis patients treated with risankizumab: a cohort study utilising large healthcare databases with mother-baby linkage in the United States [final study report expected in Q3 2026] (from initial opinion/marketing authorisation)] as per the request for supplementary information (RSI) adopted in November 2019

17.3. Results of PASS imposed in the marketing authorisation(s)⁷⁶

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁷⁷

17.4.1. Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/II/0113

Applicant: Genzyme Europe BV

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study AGALSC08994 (listed as a category 3 study in the RMP): a post-authorisation study on Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey of healthcare providers and patients/caregivers. The RMP (version 2.0) is updated accordingly. The RMP is also updated in line with revision 2 of the guidance on the format of RMP in the EU (template) and with information on study AGAL02603: a multicentre, multinational study of the effects of Fabrazyme (agalsidase beta) treatment on lactation and infants and study AGAL19211: the Fabry registry/pregnancy sub-registry

17.4.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/II/0079

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report from study ALGMYC07390: prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions to test the effectiveness of the approved Safety Information Packet (SIP) (in fulfilment of MEA 053)

17.4.3. Anakinra - KINERET (CAP) - EMEA/H/C/000363/II/0073

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final report from study Sobi.ANAKIN-302 (listed as a category 3 study in the RMP): a non-interventional PASS to evaluate the long-term safety of Kineret (anakinra) in patients with systemic juvenile idiopathic arthritis. The RMP (version 5.1) is updated accordingly

⁷⁶ In accordance with Article 107p-q of Directive 2001/83/EC

⁷⁷ 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

17.4.4. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0063/G

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of the submission of the final reports from studies IM103075 and IM103076 (listed as category 3 studies in the RMP). Study IM103075 is a prospective cohort study to assess the association between belatacept use and risk of post-transplant lymphoproliferative disorder (PTLD) in renal transplant recipients in the United States (US). Study IM103076 is a prospective patient registry study to estimate the incidence rates of confirmed PTLD, central nervous system (CNS) PTLD and progressive multifocal leukoencephalopathy (PML) in adult renal transplant recipients treated with belatacept in the US. The RMP (version 17.2) is updated accordingly and includes some administrative updates

17.4.5. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1742/0037; FORXIGA (CAP) - EMEA/H/C/002322/WS1742/0056; dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/WS1742/0043; XIGDUO (CAP) - EMEA/H/C/002672/WS1742/0054

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.4 of the SmPC based on the final results of a PASS (listed as a category 3 study in the RMPs): a meta-analysis across the following studies: 1) study D1690C00018: a 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled, phase 3 study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and hypertension who exhibit inadequate glycaemic control on usual care; 2) study D1690C00019: A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM and CVD, who exhibit inadequate glycaemic control on usual care; 3) study D1693C00001 (DECLARE): a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with T2DM, for analysis of lower limb amputation and relevant preceding adverse events. The package leaflets are updated accordingly. In addition, the MAH took the opportunity to implement a minor editorial change in the product information of Edistride (dapagliflozin). The RMPs (version 19 for Edistride/Forxiga (dapagliflozin) and version 12 for Ebymect/Xigduo (dapagliflozin/metformin) are updated accordingly

17.4.6. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/II/0048

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final study report from study B010 (listed as a category 3 study in the RMP) investigating the utilisation of dulaglutide in European countries: a cross-sectional, multi-country and multi-source drug utilisation study using electronic health

record databases (in fulfilment of MEA 001). The RMP (version 5.1) is updated accordingly

17.4.7. Maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/II/0061

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study A4001067 (POEM) (listed as a category 3 study in the RMP): a non-interventional international, multicentre, prospective observational study of the safety of maraviroc used with optimised background therapy in treatment-experienced human immunodeficiency virus 1 (HIV-1) infected patients. The RMP (version 12.0) is updated accordingly

17.4.8. Tocilizumab - ROACTEMRA (CAP) - EMEA/H/C/000955/II/0094

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Submission of the final report from study WA22480 (listed as a category 3 study in the RMP): a phase 4, prospective observational cohort study using Sweden registers to provide long term safety data from the use of tocilizumab in Sweden for rheumatoid arthritis (RA) patients (ARTIS⁷⁸)

17.4.9. Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/WS1761/0028; ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/WS1761/0013 Umeclidinium, vilanterol - ANORO ELLIPTA (CAP) - EMEA/H/C/002751/WS1761/0029; LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/003754/WS1761/0032

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of the final report from study WWE117397 (listed as a category 3 study in the RMP): a retrospective longitudinal non-interventional observational study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) or new users of long-acting bronchodilators (LABD) in the primary care setting

17.4.10. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0074/G

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding acute phase reactions as requested in the conclusions of post-authorisation measure LEG 0037 on 'rheumatological/immune-mediated syndrome (RIMS)' finalised in September 2019; 2) update of section 5.1 of the SmPC in following the assessment of 24 month data from paediatric extension study 2337E1: a one

⁷⁸ Anti-Rheumatic Therapy In Sweden (Swedish biologics register)

year, multicentre, open-label extension to study CZOL446H2337 to evaluate safety and efficacy of zoledronic acid twice yearly in osteoporotic children treated with glucocorticoids submitted in accordance with Article 46. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1)

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

17.5.1. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.12

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report 2019 on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.12

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report 2019 on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, multicentre, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease irrespective of treatment status. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children

17.5.3. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/MEA 017.5

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Third interim report for study ALIROC07997: a PASS using healthcare databases to monitor the safety of Praluent (alirocumab) in patients affected with the human immunodeficiency virus (HIV) (from initial opinion/marketing authorisation)

17.5.4. Deferasirox - EXJADE (CAP) - EMEA/H/C/000670/ANX 038.11

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Sixth annual interim report for study CICL670E2422: an observational, multicentre

cohort study to evaluate the long-term exposure and safety of deferasirox in the treatment of paediatric non-transfusion dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate

17.5.5. Eculizumab - SOLIRIS (CAP) - EMEA/H/C/000791/MEA 062

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

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

17.5.6. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in: Q4/2021]

17.5.7. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in: Q4/2021]

17.5.8. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third interim report for enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR) expected in: Q4/2021]

17.5.9. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 024

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Interim results for study E7389-M044-504 (IRENE): an observational, post-authorisation, single-arm, prospective, multicentre cohort study to characterise and determine the incidence of eribulin-induced peripheral neuropathy (PN), and the frequency and time to resolution of eribulin-induced PN in adult patients treated with eribulin in a real-life setting with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease

17.5.10. Florbetaben (¹⁸F) - NEURACEQ (CAP) - EMEA/H/C/002553/MEA 001.9

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Martin Huber

Scope: Second interim report for study FBB-01_03_13 (PASS 2): a non-interventional/observational, cross-sectional, retrospective, multicentre, multi-country registry to observe usage pattern, safety and tolerability of the diagnostic agent NeuraCeq (florbetaben (¹⁸F)) in European clinical practice [final clinical study report (CSR) expected in Q2/2020]

17.5.11. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/LEG 188.6

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Annual reports for 2018 and 2019 on a review of second primary malignancies (SPM), including a data analysis plan, in order to compare incidence rates of SPM among patients treated with Glivec (imatinib) with expected incidence based on the rates among the general population, including MAH's response to LEG 188.5 on annual report for 2017 as per the request for supplementary information (RSI) adopted in March 2018

17.5.12. Imatinib - GLIVEC (CAP) - EMEA/H/C/000406/ANX 191.8

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

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

17.5.13. Insulin glargine, lixisenatide - SULIQUA (CAP) - EMEA/H/C/004243/MEA 005.2

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Menno van der Elst

Scope: Third annual progress report for a patient registry of lixisenatide use in adult

patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report expected in December 2020] (from initial opinion/marketing authorisation)

17.5.14. Lixisenatide - LYXUMIA (CAP) - EMEA/H/C/002445/MEA 008.4

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Annika Folin

Scope: Third annual progress report for a patient registry of lixisenatide use in adult patients with type 2 diabetes mellitus (T2DM) (listed as a category 3 study in the RMP) in order to monitor the occurrence of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult T2DM patients treated with lixisenatide using data from national registers and databases in Italy and Belgium [final report expected in December 2020] (from initial opinion/marketing authorisation)

17.5.15. Lutetium (¹⁷⁷Lu) oxodotreotide - LUTATHERA (CAP) - EMEA/H/C/004123/MEA 001.3

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Adam Przybylkowski

Scope: First progress report for study A-LUT-T-E02-402 (SALUS study) (listed as a category 3 study in the RMP): an international post-authorisation safety registry to assess the long-term safety of Lutathera (lutetium (¹⁷⁷Lu)) for unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) [final clinical study report (CSR) expected in December 2025]

17.5.16. Nonacog beta pegol - REFIXIA (CAP) - EMEA/H/C/004178/LEG 006

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Study progress report for PASS NN7999-4031 : a non-interventional study in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs

17.5.17. Pitolisant - WAKIX (CAP) - EMEA/H/C/002616/ANX 001.2

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Second annual interim study report for study P15-11: a multicentre, observational PASS to document the drug utilisation of Wakix (pitolisant) and to collect information on the safety of Wakix (pitolisant) when used in routine medical practice [final results expected in 2023] (from opinion/marketing authorisation)

17.5.18. Tezacaftor, ivacaftor - SYMKEVI (CAP) - EMEA/H/C/004682/MEA 002.2

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Rhea Fitzgerald

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

17.5.19. Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/ANX 002.1

Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Interim report for study 156-12-299: a non-interventional PASS to investigate the risks of hepatotoxicity, basal cell carcinoma and glaucoma associated with the use of Jinarc (tolvaptan). In addition, the study investigates pregnancy outcomes in patients treated with Jinarc (tolvaptan), patterns of medicinal product utilisation especially with regards to off-label use and use in patients over 50 years old as well as adverse drug reactions (ADRs) associated with long term use of Jinarc (tolvaptan) [final clinical study report (CSR) expected by: Q1/2026]

17.5.20. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/MEA 002.6

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Eva Jirsová

Scope: Annual study progress report and first interim analysis report for study P16-562 (listed as a category 3 study in the RMP): a prospective observational study to assess the long-term safety profile of venetoclax in a Swedish cohort of chronic lymphocytic leukaemia (CLL) patients

17.6. Others

17.6.1. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/MEA 062

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Feasibility report for an international, exploratory, retrospective non-interventional study to collect long-term safety data including malignancies in children with growth failure who have received at least 3 years of Increlex (mecasermin) therapy and followed at least 5 years after the end of Increlex (mecasermin) treatment (from variation II/60 concluded in November 2019)

17.6.2. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060.2

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 060.1 [six-monthly summary report of medication error events reported with the on body injector in the EU market, as requested in the conclusions of variation II/093/G finalised in February 2018] as per the request for supplementary information (RSI) adopted in October 2019

17.7. New Scientific Advice

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

17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the 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. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0031 (with RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Annual reassessment of the marketing authorisation

18.1.2. Lomitapide - LOJUXTA (CAP) - EMEA/H/C/002578/S/0036 (without RMP)

Applicant: Amryt Pharmaceuticals DAC

PRAC Rapporteur: Menno van der Elst

Scope: Annual reassessment of the marketing authorisation

18.1.3. Metreleptin - MYALEPTA (CAP) - EMEA/H/C/004218/S/0009 (with RMP)

Applicant: Aegerion Pharmaceuticals B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

18.1.4. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0055 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Cemiplimab - LIBTAYO (CAP) - EMEA/H/C/004844/R/0006 (without RMP)

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/R/0055 (without RMP)

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

18.3.2. Aripiprazole - ARIPIPRAZOLE SANDOZ (CAP) - EMEA/H/C/004008/R/0014 (without RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.3. Aripiprazole - ARIPIPRAZOLE ZENTIVA (CAP) - EMEA/H/C/003899/R/0012 (with RMP)

Applicant: Zentiva, k.s.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

18.3.4. Duloxetine - DULOXETINE ZENTIVA (CAP) - EMEA/H/C/003935/R/0009 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.5. Guanfacine - INTUNIV (CAP) - EMEA/H/C/003759/R/0022 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.6. Idebenone - RAXONE (CAP) - EMEA/H/C/003834/R/0020 (without RMP)

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.7. Isavuconazole - CRESEMBA (CAP) - EMEA/H/C/002734/R/0027 (without RMP)

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.8. Ivabradine - IVABRADINE ANPHARM (CAP) - EMEA/H/C/004187/R/0014 (with RMP)

Applicant: ANPHARM Przedsiębiorstwo Farmaceutyczne S.A.

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pemetrexed - PEMETREXED LILLY (CAP) - EMEA/H/C/004114/R/0011 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

18.3.10. Pregabalin - PREGABALIN ACCORD (CAP) - EMEA/H/C/004024/R/0015 (with RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.11. Pregabalin - PREGABALIN SANDOZ (CAP) - EMEA/H/C/004010/R/0012 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.12. Pregabalin - PREGABALIN SANDOZ GMBH (CAP) - EMEA/H/C/004070/R/0013 (with RMP)

Applicant: Sandoz GmbH

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.13. Pregabalin - PREGABALIN ZENTIVA (CAP) - EMEA/H/C/003900/R/0021 (with RMP)

Applicant: Zentiva k.s.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.14. Roflumilast - DAXAS (CAP) - EMEA/H/C/001179/R/0039 (without RMP)

Applicant: AstraZeneca AB

PRAC Rapporteur: Maria del Pilar Rayon

Scope: 5-year renewal of the marketing authorisation

18.3.15. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/R/0028 (without RMP)

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Željana Margan Koletić

Scope: 5-year renewal of the marketing authorisation

18.3.16. Sufentanil - ZALVISO (CAP) - EMEA/H/C/002784/R/0016 (without RMP)

Applicant: Grunenthal GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: 5-year renewal of the marketing authorisation

18.3.17. Velaglucerase alfa - VPRIV (CAP) - EMEA/H/C/001249/R/0045 (without RMP)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.18. Vernakalant - BRINAVESS (CAP) - EMEA/H/C/001215/R/0037 (without RMP)

Applicant: Correvio

PRAC Rapporteur: Menno van der Elst

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 09-12 March 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No participation in final deliberations and voting on:	4.3.6. Thiazide, thiazide-like diuretics and combinations 15.2.10. Telotristat ethyl - XERMELO (CAP) 16.1.23. Mecasermin - INCRELEX (CAP) 16.1.32. Telotristat - XERMELO (CAP) 17.6.1. Mecasermin - INCRELEX (CAP)
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion,	15.3.8. Ceftazidime, avibactam - ZAVICEFTA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	3.2.1. Leuprorelin (NAP) 3.3.1. Fluorouracil and related substances 4.2.1. Amitriptyline (NAP); bupropion (NAP); citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP); trazodone (NAP); venlafaxine (NAP) 4.3.1. Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP; naloxone – NYXOID (CAP), NAP; Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>imipramine (NAP); nortriptyline (NAP); trimipramine (NAP); Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP); phenelzine (NAP); selegiline (NAP); tranylcypromine (NAP);</p> <p>Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); Lithium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP);</p> <p>Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan (NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP);</p> <p>Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron - ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron - AKYNZEO (CAP); tropisetron (NAP);</p> <p>Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP)</p> <p>4.3.6. Thiazide, thiazide-like diuretics and combinations</p>
Julia Pallos	Member	Hungary	No participation in final deliberations and voting on:	4.3.6. Thiazide, thiazide-like diuretics and combinations
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	3.2.1. Leuprorelin (NAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
John Joseph Borg	Member	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	4.3.1. Buprenorphine – BUVIDAL (CAP), SIXMO (CAP), NAP; buprenorphine, naloxone – SUBOXONE (CAP), ZUBSOLV (CAP), NAP; naloxone – NYXOID (CAP), NAP; Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluvoxamine (NAP); fluoxetine (NAP); paroxetine (NAP); sertraline (NAP); Serotonin norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine (NAP); duloxetine – CYMBALTA (CAP), DULOXETINE LILLY (CAP), DULOXETINE MYLAN (CAP), DULOXETINE ZENTIVA (CAP), XERISTAR (CAP), YENTREVE (CAP), NAP; milnacipran (NAP); venlafaxine (NAP); Tricyclic antidepressants (TCAs): amitriptyline (NAP); clomipramine (NAP); doxepin (NAP); imipramine (NAP); nortriptyline (NAP); trimipramine (NAP); Monoamine oxidase inhibitors (MAOIs): isocarboxazid (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				phenelzine (NAP); selegiline (NAP); tranylcypromine (NAP); Other psychiatric medicines: amoxapine (NAP); buspirone (NAP); lthium (NAP); maprotiline (NAP); mirtazapine (NAP); trazodone (NAP); Serotonin receptor agonists: almotriptan (NAP); frovatriptan (NAP); naratriptan(NAP); rizatriptan (NAP); sumatriptan (NAP); zolmitriptan (NAP); Antiemetics: granisetron - SANCUSO (CAP), NAP; ondansetron (NAP); palonosetron – ALOXI (CAP), PALONOSETRON ACCORD (CAP), NAP; netupitant, palonosetron – AKYNZEO (CAP); tropisetron (NAP); Other serotonergic drugs: cyclobenzaprine (NAP); dextromethorphan (NAP); hypericum perforatum (NAP); linezolid (NAP); methylene blue (NAP); tryptophan (NAP) 4.3.2. Hormone replacement therapy (HRT): chlorotrianisene (NAP); conjugated estrogens (NAP); conjugated estrogens, bazedoxifene - DUAVIVE (CAP); dienestrol (NAP); diethylstilbestrol (NAP); estradiol (NAP); estradiol, norethisterone (NAP); estriol (NAP); estrone (NAP); ethinylestradiol (NAP); methallenestril (NAP); moxestrol (NAP); promestriene (NAP); tibolone (NAP) 4.3.6. Thiazide, thiazide-like diuretics and combinations 7.3.1. Rivaroxaban – XARELTO (CAP) 4

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				16.1.12. Damoctocog alfa pegol - JIVI (CAP) 7.4.2. Riociguat - ADEMPAS (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation in discussion, final deliberations and voting on:	3.1.1. Ulipristal acetate – ESMYA (CAP), NAP
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals'	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		Representative	this meeting	
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Flora Musuamba Tshinanu	Expert - via telephone *	Belgium	No interests declared	Full involvement
Helle Marie Esbjørn Kristensen	Expert - via telephone *	Denmark	No interests declared	Full involvement
Anita Vibsig Neutzsky-Wulff	Expert - via telephone *	Denmark	No interests declared	Full involvement
Annette Cleveland Nielsen	Expert - via telephone *	Denmark	No restrictions applicable to this meeting	Full involvement
Emma Louise Nautrup Ravn Stadsbjerg	Expert - via telephone *	Denmark	No interests declared	Full involvement
Lucie Sagot	Expert - via telephone *	France	No restrictions applicable to this meeting	Full involvement
Dennis Lex	Expert - via telephone *	Germany	No restrictions applicable to this meeting	Full involvement
Nils Lilienthal	Expert - via telephone *	Germany	No interests declared	Full involvement
Kerstin Lösckke	Expert - via telephone *	Germany	No interests declared	Full involvement
Jens Reinhardt	Expert - via telephone *	Germany	No interests declared	Full involvement
Martina Schüßler-Lenz	Expert - via telephone *	Germany	No restrictions applicable to this meeting	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ruchika Sharma	Expert - via telephone *	Ireland	No restrictions applicable to this meeting	Full involvement
Antonella Isgro	Expert - via telephone *	Italy	No interests declared	Full involvement
Svetlana Lorenzano	Expert - via telephone *	Italy	No restrictions applicable to this meeting	Full involvement
Giuseppa Pistrutto	Expert - via telephone *	Italy	No interests declared	Full involvement
Ineke (Hubertina Johanna Maria Josephina) Crijs	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Carla Herberts	Expert - via telephone *	Netherlands	No restrictions applicable to this meeting	Full involvement
Serena Marchetti	Expert - via telephone *	Netherlands	No restrictions applicable to this meeting	Full involvement
Johannes (Hans) Ovelgonne	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Eliesbeth Rook	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Paul ten Berg	Expert - via telephone *	Netherlands	No restrictions applicable to this meeting	Full involvement
Elizabeth (Lies) van Vlijmen	Expert - in person*	Netherlands	No interests declared	Full involvement
Anita Volkers	Expert - in person*	Netherlands	No interests declared	Full involvement
Raquel Granados	Expert - via telephone *	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	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
Carin Bergquist	Expert - via telephone *	Sweden	No interests declared	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, the 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:

<http://www.ema.europa.eu/ema/>