



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2018
EMA/PRAC/752056/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 01-04 October 2018

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

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

Disclaimers

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

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

Note on access to documents

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



Table of contents

1.	Introduction	12
1.1.	Welcome and declarations of interest of members, alternates and experts	12
1.2.	Agenda of the meeting on 01-04 October 2018	12
1.3.	Minutes of the previous meeting on 03-06 September 2018.....	12
2.	EU referral procedures for safety reasons: urgent EU procedures	12
2.1.	Newly triggered procedures	12
2.2.	Ongoing procedures	12
2.3.	Procedures for finalisation.....	12
3.	EU referral procedures for safety reasons: other EU referral procedures	13
3.1.	Newly triggered procedures	13
3.2.	Ongoing procedures	13
3.2.1.	Methotrexate - JYLAMVO (CAP); NAP - EMEA/H/A-31/1463.....	13
3.3.	Procedures for finalisation.....	13
3.3.1.	Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); piperidic acid (NAP) - EMEA/H/A-31/1452	13
3.4.	Re-examination procedures.....	15
3.5.	Others	15
4.	Signals assessment and prioritisation	16
4.1.	New signals detected from EU spontaneous reporting systems	16
4.2.	New signals detected from other sources	16
4.2.1.	Canagliflozin – INVOKANA (CAP); dapagliflozin - FORXIGA (CAP); empagliflozin - JARDIANCE (CAP); ertugliflozin – STEGLATRO (CAP).....	16
4.2.2.	Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP	17
4.3.	Signals follow-up and prioritisation.....	18
4.3.1.	Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP); infliximab – FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP).....	18
4.3.2.	Belimumab – BENLYSTA (CAP)	19
4.3.3.	Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/SDA/021; dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/SDA/010; elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/SDA/010; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/SDA/009; ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/SDA/019; ombitasvir, periteprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/SDA/012; sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/SDA/026;	

	sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/SDA/010; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/SDA/003	20
4.3.4.	Dolutegravir – TIVICAY (CAP) – EMEA/H/C/002753/SDA/009; abacavir sulfate, dolutegravir sodium, lamivudine – TRIUMEQ (CAP); dolutegravir, rilpivirine – JULUCA (CAP)	21
4.3.5.	Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, nomegestrol acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP).....	22
4.3.6.	Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, nomegestrol acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP).....	23
4.3.7.	Oxybutynin – KENTERA (CAP), NAP; carbamazepine (NAP)	25
4.3.8.	Teriflunomide – AUBAGIO (CAP) - EMEA/H/C/002514/SDA/004.....	25
4.3.9.	Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/SDA/101, HERZUMA (CAP) - EMEA/H/C/002575/SDA/002, ONTRUZANT (CAP) - EMEA/H/C/004323/SDA/003; trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/SDA/020; pertuzumab – PERJETA (CAP) - EMEA/H/C/002547/SDA/013.....	26

5. Risk management plans (RMPs) 27

5.1.	Medicines in the pre-authorisation phase	27
5.1.1.	Botulinum toxin type A - EMEA/H/C/004587.....	27
5.1.2.	Dapivirine - Art 58 - EMEA/H/W/002168.....	27
5.1.3.	Lorlatinib - EMEA/H/C/004646.....	27
5.1.4.	Lusutrombopag - EMEA/H/C/004720.....	27
5.1.5.	Treosulfan - EMEA/H/C/004751, Orphan.....	27
5.1.6.	Zanamivir - EMEA/H/C/004102.....	28
5.2.	Medicines in the post-authorisation phase – PRAC-led procedures.....	28
5.2.1.	Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0148	28

5.2.2.	Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/II/0013, Orphan	29
5.3.	Medicines in the post-authorisation phase – CHMP-led procedures	30
5.3.1.	Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1344/0025; FORXIGA (CAP) - EMEA/H/C/002322/WS1344/0044.....	30
5.3.2.	Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0092	31
6.	Periodic safety update reports (PSURs)	32
6.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	32
6.1.1.	Apremilast - OTEZLA (CAP) - PSUSA/00010338/201803	32
6.1.2.	Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201803	33
6.1.3.	Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201803	33
6.1.4.	Velaglucerase alfa - VPRIV (CAP) - PSUSA/00003103/201802	34
6.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	35
6.2.1.	Estradiol, noregestrol acetate - ZOELY (CAP); NAP - PSUSA/00002182/201801	35
6.2.2.	Pemetrexed - ALIMTA (CAP); ARMISARTE (CAP); NAP - PSUSA/00002330/201802	36
6.2.3.	Voriconazole - VFEND (CAP); NAP - PSUSA/00003127/201802.....	37
6.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	38
6.3.1.	Bilastine (NAP) - PSUSA/00003163/201803	38
6.3.2.	Cilazapril (NAP); cilazapril, hydrochlorothiazide (NAP) - PSUSA/00000749/201802	38
6.3.3.	Ciprofloxacin (NAP) - PSUSA/00000775/201801	39
6.3.4.	Lorazepam (NAP) - PSUSA/00001909/201801.....	40
6.3.5.	Noregestrol (NAP) - PSUSA/00002181/201801	42
6.4.	Follow-up to PSUR/PSUSA procedures	42
6.4.1.	Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/LEG 038	42
7.	Post-authorisation safety studies (PASS)	43
7.1.	Protocols of PASS imposed in the marketing authorisation(s).....	43
7.1.1.	Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032	43
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	44
7.3.	Results of PASS imposed in the marketing authorisation(s).....	44
7.3.1.	Amino acid combinations, glucose, triglyceride combinations, with or without electrolytes, mineral compounds (NAP) - EMEA/H/N/PSR/S/0017	44
7.4.	Results of PASS non-imposed in the marketing authorisation(s).....	45
7.4.1.	Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0069	45
7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	46
7.6.	Others	46
7.7.	New Scientific Advice	46

7.8.	Ongoing Scientific Advice	47
7.9.	Final Scientific Advice (Reports and Scientific Advice letters)	47
8.	Renewals of the marketing authorisation, conditional renewal and annual reassessments	47
8.1.	Annual reassessments of the marketing authorisation	47
8.2.	Conditional renewals of the marketing authorisation	47
8.3.	Renewals of the marketing authorisation	47
9.	Product related pharmacovigilance inspections	47
9.1.	List of planned pharmacovigilance inspections	47
9.2.	Ongoing or concluded pharmacovigilance inspections	47
9.3.	Others	47
10.	Other safety issues for discussion requested by the CHMP or the EMA	47
10.1.	Safety related variations of the marketing authorisation.....	47
10.1.1.	Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0073	47
10.2.	Timing and message content in relation to Member States' safety announcements	49
10.3.	Other requests.....	49
10.4.	Scientific Advice	49
11.	Other safety issues for discussion requested by the Member States	49
11.1.	Safety related variations of the marketing authorisation.....	49
11.2.	Other requests.....	49
11.2.1.	Dienogest, ethinylestradiol (NAP) - DE/H/xxxx/WS/534.....	49
11.2.2.	Finasteride (NAP) - SE/H/xxxx/WS/243	51
11.2.3.	Minocycline (NAP) - ES/H/PSUFU/00002065/201708.....	52
12.	Organisational, regulatory and methodological matters	52
12.1.	Mandate and organisation of the PRAC	52
12.2.	Coordination with EMA Scientific Committees or CMDh-v	52
12.3.	Coordination with EMA Working Parties/Working Groups/Drafting Groups	52
12.4.	Cooperation within the EU regulatory network.....	53
12.4.1.	Brexit: preparedness of the regulatory network and capacity increase.....	53
12.4.2.	Regulatory science engagement plan to 2025.....	53
12.5.	Cooperation with International Regulators.....	53
12.6.	Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee.....	53
12.7.	PRAC work plan	53
12.8.	Planning and reporting	53

12.8.1.	Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q3 2018	53
12.9.	Pharmacovigilance audits and inspections	53
12.9.1.	Pharmacovigilance systems and their quality systems	53
12.9.2.	Pharmacovigilance inspections	54
12.9.3.	Pharmacovigilance audits.....	54
12.10.	Periodic safety update reports (PSURs) & Union reference date (EURD) list	54
12.10.1.	Periodic safety update reports	54
12.10.2.	Granularity and Periodicity Advisory Group (GPAG)	54
12.10.3.	PSURs repository	54
12.10.4.	Union reference date list – consultation on the draft list	54
12.11.	Signal management	54
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group	54
12.12.	Adverse drug reactions reporting and additional monitoring.....	55
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	55
12.12.2.	Additional monitoring	55
12.12.3.	List of products under additional monitoring – consultation on the draft list	55
12.13.	EudraVigilance database.....	55
12.13.1.	Activities related to the confirmation of full functionality	55
12.14.	Risk management plans and effectiveness of risk minimisations.....	55
12.14.1.	Risk management plan (RMP) template for industry - revision	55
12.14.2.	Risk management systems	55
12.14.3.	Risk minimisation measures: Patient alert cards and patient reminder cards - clarification	55
12.14.4.	Tools, educational materials and effectiveness measurement of risk minimisations	56
12.15.	Post-authorisation safety studies (PASS)	56
12.15.1.	Post-authorisation Safety Studies – imposed PASS	56
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS	56
12.16.	Community procedures.....	56
12.16.1.	Referral procedures for safety reasons	56
12.17.	Renewals, conditional renewals, annual reassessments	56
12.18.	Risk communication and transparency	56
12.18.1.	Public participation in pharmacovigilance	56
12.18.2.	Safety communication	56
12.19.	Continuous pharmacovigilance	56
12.19.1.	Incident management	56
12.20.	Others	57
12.20.1.	Guideline on good pharmacovigilance practices (GVP) Product- or Population- Specific considerations III: risk management in pregnant and breastfeeding women - Update	57

13.	Any other business	57
14.	Annex I – Signals assessment and prioritisation	57
14.1.	New signals detected from EU spontaneous reporting systems	57
14.1.1.	Avelumab – BAVENCIO (CAP)	57
14.1.2.	Tocilizumab – ROACTEMRA (CAP)	57
14.2.	New signals detected from other sources	58
15.	Annex I – Risk management plans	58
15.1.	Medicines in the pre-authorisation phase	58
15.1.1.	Tobramycin - EMEA/H/C/005086	58
15.2.	Medicines in the post-authorisation phase – PRAC-led procedures	58
15.2.1.	Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0030	58
15.2.2.	Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/WS1441/0034; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/WS1441/0051; emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/WS1441/0035; tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/WS1441/0016	58
15.2.3.	Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0028	59
15.2.4.	Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0063	59
15.2.5.	Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1364/0092; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1364/0021	59
15.3.	Medicines in the post-authorisation phase – CHMP-led procedures	60
15.3.1.	Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0042	60
15.3.2.	Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0106/G	60
15.3.3.	Cetuximab - ERBITUX (CAP) - EMEA/H/C/000558/II/0082	60
15.3.4.	Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan	61
15.3.5.	Efmoroctocog alfa - ELOCTA (CAP) - EMEA/H/C/003964/II/0026	61
15.3.6.	Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0002	61
15.3.7.	Eptacog alfa (activated) - NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0104	62
15.3.8.	Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0073/G	62
15.3.9.	Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - EMEA/H/C/000739/II/0068	62
15.3.10.	Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0035	62
15.3.11.	Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0036	63
15.3.12.	Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0016/G	63
15.3.13.	Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0046	63
15.3.14.	Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0057	64
15.3.15.	Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0058	64
15.3.16.	Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0031/G, Orphan	64
15.3.17.	Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0027	64
15.3.18.	Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/X/0006/G	65
15.3.19.	Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0027	65

15.3.20.	Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0056, Orphan	65
15.3.21.	Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0028	66
15.3.22.	Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0034	66

16. Annex I - Periodic safety update reports (PSURs) 66

16.1.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only	66
16.1.1.	5-aminolevulinic acid - GLIOLAN (CAP) - PSUSA/00000009/201803	66
16.1.2.	Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201803	67
16.1.3.	Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201803	67
16.1.4.	Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201803	67
16.1.5.	Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201803	67
16.1.6.	Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201803	67
16.1.7.	Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201803	67
16.1.8.	Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201803	67
16.1.9.	Cholic acid - KOLBAM (CAP) - PSUSA/00010182/201803	68
16.1.10.	Ciclosporin - IKERVIS (CAP) - PSUSA/00010362/201803	68
16.1.11.	Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201803	68
16.1.12.	Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201803	68
16.1.13.	Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201803	68
16.1.14.	Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201803	68
16.1.15.	Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201803	68
16.1.16.	Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201803	69
16.1.17.	Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - PSUSA/00010653/201803	69
16.1.18.	Glycopyrronium - SIALANAR (CAP) - PSUSA/00010529/201803	69
16.1.19.	Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201803	69
16.1.20.	Guselkumab - TREMFYA (CAP) - PSUSA/00010652/201803	69
16.1.21.	Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201803	69
16.1.22.	Influenza vaccine (split virion, inactivated) - INTANZA (CAP) - PSUSA/00001743/201803	70
16.1.23.	Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201803	70
16.1.24.	Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201803	70
16.1.25.	Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201803	70
16.1.26.	Lapatinib - TYVERB (CAP) - PSUSA/00001829/201803	70
16.1.27.	Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201803	70
16.1.28.	Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201803	70
16.1.29.	Niraparib - ZEJULA (CAP) - PSUSA/00010655/201803	71
16.1.30.	Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201803	71

16.1.31.	Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201803	71
16.1.32.	Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58) - EMEA/H/W/002300/PSUV/0033	71
16.1.33.	Tobramycin - VANTOBRA (CAP) - PSUSA/00010370/201803	71
16.1.34.	Tolcapone - TASMAR (CAP) - PSUSA/00002985/201803	71
16.1.35.	Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201803	72
16.1.36.	Vildagliptin - GALVUS (CAP); JALRA (CAP); XILIARX (CAP); vildagliptin, metformin - EUCREAS (CAP); ICANDRA (CAP) ; ZOMARIST (CAP) - PSUSA/00003113/201802	72
16.2.	PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....	72
16.2.1.	Atosiban - TRACTOCILE (CAP); NAP - PSUSA/00000264/201801	72
16.2.2.	Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201802	72
16.2.3.	Trientine - CUPRIOR (CAP); NAP - PSUSA/00010637/201803.....	72
16.3.	PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....	72
16.3.1.	Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201802.....	72
16.3.2.	Argatroban (NAP) - PSUSA/00009057/201801	73
16.3.3.	Cilostazol (NAP) - PSUSA/00010209/201802.....	73
16.3.4.	Ciprofloxacin (NAP) - PSUSA/00000776/201801	73
16.3.5.	Dacarbazine (NAP) - PSUSA/00000919/201802.....	73
16.3.6.	Ethinylestradiol, gestodene (NAP) - PSUSA/00010145/201802	73
16.3.7.	Fenoterol, ipratropium (NAP) - PSUSA/00001367/201802.....	73
16.3.8.	Human coagulation factor VIII (NAP) - PSUSA/00009174/201802.....	73
16.3.9.	Hydrochlorothiazide, losartan (NAP) - PSUSA/00001655/201802.....	74
16.3.10.	Hydroxyethyl starch (NAP) - PSUSA/00001694/201803.....	74
16.3.11.	Iloprost (NAP) - PSUSA/00009190/201801	74
16.3.12.	Lisdexamfetamine (NAP) - PSUSA/00010289/201802.....	74
16.3.13.	Lomustine (NAP) - PSUSA/00001902/201801.....	74
16.3.14.	Mivacurium (NAP) - PSUSA/00002077/201801.....	74
16.3.15.	Nafarelin (NAP) - PSUSA/00002105/201802	74
16.3.16.	Olodaterol (NAP) - PSUSA/00010245/201803.....	75
16.3.17.	Tauroselcholic [⁷⁵ Se] acid (NAP) - PSUSA/00010486/201801	75
16.4.	Follow-up to PSUR/PSUSA procedures	75
17.	Annex I – Post-authorisation safety studies (PASS)	75
17.1.	Protocols of PASS imposed in the marketing authorisation(s).....	75
17.1.1.	Chlormadinone acetate, ethinylestradiol (NAP) - EMEA/H/N/PSA/J/0030.1	75
17.1.2.	Tolvaptan – JINARC (CAP) - EMEA/H/C/PSA/S/0031	75
17.1.3.	Velmanase alfa – LAMZEDE (CAP) - EMEA/H/C/PSP/S/0060.1	76
17.2.	Protocols of PASS non-imposed in the marketing authorisation(s)	76

17.2.1.	Agalsidase beta - FABRAZYME (CAP) - EMEA/H/C/000370/MEA 060.4	76
17.2.2.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 003.2	76
17.2.3.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 004.2	76
17.2.4.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 005.2	77
17.2.5.	Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035	77
17.2.6.	Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 012.1.....	77
17.2.7.	Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 024.1	78
17.2.8.	Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 011.1.....	78
17.2.9.	Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 014.1	79
17.2.10.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.6	79
17.2.11.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.2	79
17.2.12.	Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 003.2	80
17.2.13.	Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.2	80
17.2.14.	Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.3	80
17.2.15.	Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007.2	81
17.2.16.	Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.1	81
17.2.17.	Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.2	81
17.3.	Results of PASS imposed in the marketing authorisation(s).....	82
17.3.1.	Ivabradine – CORLENTOR (CAP), IVABRADINE ANPHARM (CAP), PROCORALAN (CAP); NAP - EMEA/H/C-N/PSR/S/0019	82
17.4.	Results of PASS non-imposed in the marketing authorisation(s).....	82
17.4.1.	Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0117	82
17.4.2.	Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.4	82
17.4.3.	Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.4	82
17.4.4.	Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0030.....	83
17.4.5.	Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0147	83
17.4.6.	Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0049.....	83
17.4.7.	Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0050.....	83
17.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	83
17.5.1.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.5	83
17.5.2.	Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.1	84
17.5.3.	Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.2	84
17.5.4.	Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.4	84
17.5.5.	Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.4	84
17.5.6.	Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.7.....	85
17.5.7.	Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.5.....	85
17.5.8.	Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.9	85
17.5.9.	Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.6	85

17.5.10.	Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.4	85
17.5.11.	Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.3	86
17.5.12.	Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.8	86
17.6.	Others	86
17.6.1.	Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/MEA 001.....	86
17.6.2.	Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 003	86
17.6.3.	Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 004	87
17.7.	New Scientific Advice	87
17.8.	Ongoing Scientific Advice	87
17.9.	Final Scientific Advice (Reports and Scientific Advice letters)	87
18.	Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments	87
18.1.	Annual reassessments of the marketing authorisation	87
18.1.1.	Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0059 (without RMP)	87
18.2.	Conditional renewals of the marketing authorisation	88
18.2.1.	Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0021 (with RMP)	88
18.2.2.	Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0009 (without RMP).....	88
18.2.3.	Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0032 (without RMP).....	88
18.3.	Renewals of the marketing authorisation	88
18.3.1.	Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/R/0040 (with RMP).....	88
18.3.2.	Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/R/0042 (with RMP).....	88
18.3.3.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/R/0039 (without RMP)	88
18.3.4.	Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/R/0024 (without RMP)	89
18.3.5.	Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/R/0040 (with RMP)	89
18.3.6.	Indacaterol, glycopyrronium - ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/R/0028 (without RMP)	89
18.3.7.	Mifamurtide - MEPACT (CAP) - EMEA/H/C/000802/R/0047 (without RMP)	89
18.3.8.	Para-aminosalicylic acid - GRANUPAS (CAP) - EMEA/H/C/002709/R/0026 (without RMP) ..	89
18.3.9.	Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/R/0025 (without RMP)	89
18.3.10.	Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/R/0032 (without RMP).....	89
19.	Annex II – List of participants	90
20.	Annex III - List of acronyms and abbreviations	101
21.	Explanatory notes	101

1. Introduction

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

The Chairperson opened the 01-04 October 2018 meeting by welcoming all participants.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the [Rules of Procedure](#). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Liana Gross-Martirosyan as the new alternate for the Netherlands and Ronan Grimes as the new alternate for Ireland.

1.2. Agenda of the meeting on 01-04 October 2018

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 03-06 September 2018

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

Post-meeting note: the PRAC minutes of the meeting held on 03-06 September 2018 were published on the EMA website on 26 October 2018 ([EMA/PRAC/675727/2018](#)).

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

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

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

3.1. Newly triggered procedures

None

3.2. Ongoing procedures

3.2.1. Methotrexate¹ - JYLAMVO (CAP); NAP - EMEA/H/A-31/1463

Applicants: Therakind Limited (Jylamvo), various

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

Scope: Review of the benefit-risk balance following notification by Spain 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 methotrexate-containing medicines (oral and parenteral formulations) following reports of overdose toxicity as a consequence of daily intake in error instead of weekly intake. The ongoing review also assesses the risk minimisation measures taken nationally over recent years to fully elucidate the issue and to take appropriate measures. For further background see [PRAC minutes April 2018](#).

Summary of recommendation(s)/conclusions

- The PRAC discussed the assessment reports prepared by the Rapporteurs.
- The PRAC adopted a list of outstanding issues (LoOI) to be addressed by the MAHs for methotrexate-containing medicinal products together with a revised timetable for conducting the review ([EMA/PRAC/199744/2018 Rev 1](#)).

3.3. Procedures for finalisation

3.3.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452

Applicant(s): Chiesi Farmaceutici S.p.A. (Quinsair), various

PRAC Rapporteur: Eva Jirsová; PRAC Co-rapporteur: Martin Huber

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

¹ For oral use

A referral procedure under Article 31 of Directive 2001/83/EC is to be concluded for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, assessing the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of serious long-lasting and potentially irreversible side effects mainly affecting musculoskeletal and nervous systems. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable. For further background, see [PRAC minutes February 2017](#), [PRAC minutes June 2017](#), [PRAC minutes October 2017](#), [PRAC minutes November 2017](#), [PRAC minutes February 2018](#), [PRAC minutes March 2018](#), [PRAC minutes May 2018](#), [PRAC minutes June 2018](#) and [PRAC minutes July 2018](#).

Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

The PRAC considered the totality of the data submitted for medicinal products containing quinolones and fluoroquinolones with regard to long-lasting, disabling and potentially irreversible adverse drug reactions (ADRs). This included the responses submitted by the MAHs in writing as well as the outcomes of consultations with the Infectious Disease Working Party ([IDWP](#)). In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing. The PRAC also reviewed all data submitted by different stakeholders, both before and after the public hearing.

The PRAC concluded that some of the serious adverse drug reactions associated with the use of quinolones and fluoroquinolones could very rarely be long-lasting, disabling and potentially irreversible and that these risks are a class effect.

The PRAC concluded that for patients with a serious infection that is susceptible to these antibiotics fluoroquinolones remain an important treatment option despite the very rare risk of long-lasting, disabling and potentially irreversible adverse reactions

In addition, the PRAC concluded that in case of milder infections, other treatment options should be considered. Therefore fluoroquinolones should be reserved as a last line treatment in patients where other therapeutic options are not effective or not tolerated.

The PRAC also concluded that in case of mild and/or self-limiting infections, the benefit of quinolones and fluoroquinolones treatment does not outweigh the overall risk related to the use of these medicinal products including serious risk of long-lasting, disabling and potentially irreversible adverse drug reactions.

As a consequence, the PRAC recommended the suspension of the following quinolone-medicinal products containing nalidixic acid, pipemidic acid, cinoxacin and flumequine, as they do not retain any indication with a positive benefit-risk. To lift the suspension the MAHs should submit appropriate scientific evidence to demonstrate a positive benefit-risk balance of the medicinal products. Also, the PRAC recommended changes to the product information including the indication and further warnings and precautions of use relating to the long-lasting, disabling and potentially irreversible adverse drug reactions.

Core elements for a direct healthcare professional communication (DHPC) were agreed, together with the timelines for its distribution.

The PRAC further agreed on the need for a detailed follow-up of all incoming spontaneously reported cases of prolonged, potentially irreversible, serious suspected adverse drug

reactions to fluoroquinolones, a cumulative review of all these cases as part of the next PSUR submissions, and a harmonisation of the PSUR submission dates for fluoroquinolones.

Also, a drug utilisation study (independent, EMA-funded) to investigate changes in prescribing behaviour in the outpatient setting will be performed.

In view of the above, the PRAC concluded that the benefit-risk balance of the following fluoroquinolone-medicinal products containing pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin remains favourable subject to the agreed amendments to the product information and other risk minimisation measures. The Committee, as a consequence, recommended the variation to the terms of the marketing authorisations for pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin.

The PRAC also concluded that the benefit-risk balance of the following medicinal products containing nalidixic acid, piperidic acid, cinoxacin and flumequine is no longer favourable and should be suspended. To lift the suspension, the PRAC recommended that the MAHs should submit the appropriate scientific evidence to demonstrate a positive benefit-risk of the medicinal product in any indication.

Summary of recommendation(s)/conclusions

- The PRAC adopted, by written procedure on 16 October 2018, a recommendation to vary the terms of the marketing authorisations for pefloxacin-, lomefloxacin-, ciprofloxacin-, levofloxacin-, ofloxacin-, moxifloxacin-, norfloxacin-, prulifloxacin-, rufloxacin-containing medicinal products; and to suspend the marketing authorisations of nalidixic acid, piperidic acid-, cinoxacin- and flumequine-containing medicinal products. The above-mentioned PRAC recommendation is to be considered by CHMP for an opinion – see EMA Press Release ([EMA/ 668915/2018](#)) entitled 'Fluoroquinolone and quinolone antibiotics: PRAC recommends restrictions on use - New restrictions follow review of disabling and potentially long-lasting side effects'.
- The PRAC agreed on the distribution of a DHPC together with a communication plan.

Post-meeting note: the press release titled 'disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics' ([EMA/795349/2018](#)) representing the opinion adopted by the CHMP was published on the EMA website on 16/11/2018.

3.4. Re-examination procedures²

None

3.5. Others

None

² Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

4. Signals assessment and prioritisation³

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. Canagliflozin – INVOKANA (CAP); dapagliflozin - FORXIGA (CAP); empagliflozin - JARDIANCE (CAP); ertugliflozin – STEGLATRO (CAP)

Applicant(s): AstraZeneca AB (Forxiga), Boehringer Ingelheim International GmbH (Jardiance), Janssen-Cilag International NV (Invokana), Merck Sharp & Dohme B.V. (Steglatro)

PRAC Rapporteur: Martin Huber

Scope: Signal of Fournier's gangrene

EPITT 19308 – New signal

Lead Member State(s): ES, SE, DE, NL, UK

Background

Invokana, Forxiga, Jardiance and Steglatro are centrally authorised products containing respectively canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (sodium-glucose cotransporter-2 (SGLT-2) inhibitor) and are indicated in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy or as add-on therapy.

The exposure for Invokana (canagliflozin) is estimated to have been more than 3,166,534 person-years worldwide, in the period from first authorisation in 2013 to 2018. The exposure for Forxiga (dapagliflozin) is estimated to have been more than 2,995,081 patient-years, in the period from first authorisation in 2012 to 2017. The exposure for Jardiance (empagliflozin) is estimated to have been more than 3,097,527 patient-years, in the period from first authorisation in 2014 to 2018. The exposure for Steglatro (ertugliflozin) is estimated to have been more than 9,732 patient-years, in the period from first authorisation in 2017 to 2018.

In the context of the review of 12 post-marketing cases of Fournier's gangrene (necrotising fasciitis of the perineum) associated with SGLT2-inhibitors by FDA⁴ and based on 52 individual case safety reports (ICSRs) with SGLT-2 identified via EudraVigilance reported as suspected or interacting medicinal product with relevant⁵ MedDRA PTs⁶, a signal of Fournier's

³ 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

⁴ FDA Drug Safety Communication: FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. 29 August 2018 <https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm>

⁵ necrotising fasciitis, necrotising fasciitis fungal, necrotising fasciitis staphylococcal, necrotising fasciitis streptococcal, necrotising soft tissue infection, fasciitis, fascial infection, perineal abscess, perineal necrosis, perineal infection, perineal cellulitis, perineal operation, scrotal abscess, scrotal gangrene, vulval abscess, vulval cellulitis

⁶ Medical dictionary for regulatory activities – Preferred Terms

gangrene was identified by EMA. Germany confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Based on the assessment of the available data sources (i.e. FDA, literature, EudraVigilance), the PRAC considered that the most recent data demonstrates an association between Fournier's gangrene and SGLT-2 inhibitors. Therefore, the PRAC agreed that the product information for Invokana (canaglifozin), Forxiga (dapaglifozin), Jardiance (empaglifozin) and Steglatro (ertuglifozin) should be updated accordingly. Therefore the MAHs for the SGLT-2 inhibitors products should provide comments on the proposals to update their product information.

The PRAC appointed Martin Huber as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for Invokana (canaglifozin), Forxiga (dapaglifozin), Jardiance (empaglifozin) and Steglatro (ertuglifozin) should submit to EMA, within 30 days, their comments on the proposal to update the product information of SGLT-2 inhibitors including their views on the frequency of these events and for the inclusion of Fournier's Gangrene as an undesirable effect in the product information.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP

Applicant(s): Eli Lilly Nederland B.V. (Zypadhera, Zyprexa, Zyprexa Velotab), Krka, d.d. (Zalasta), various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of gestational diabetes

EPITT 19306 – New signal

Lead Member State(s): FI

Background

Olanzapine is an antipsychotic, antimanic and mood stabilising agent. Zalasta, a centrally authorised medicinal product containing olanzapine, is indicated for the treatment of schizophrenia, the treatment of moderate to severe manic episode, and, in patients whose manic episode has responded to olanzapine treatment, for the prevention of recurrence in patients with bipolar disorder. Zypadhera, a centrally authorised medicinal product containing olanzapine, is indicated for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine. Zyprexa and Zyprexa Velotab, centrally authorised medicinal products containing olanzapine are indicated for the treatment of schizophrenia, for the treatment of moderate to severe manic episode and, in patients whose manic episode has responded to olanzapine treatment, for the prevention of recurrence in patients with bipolar disorder.

Olanzapine is estimated to have been used by more than 50,796,000 patients worldwide, in the period from 1996 to 2016.

Following the publication in by *Park et al.*⁷, a signal of gestational diabetes was identified by Finland, suggesting that olanzapine continuation during pregnancy could be associated with increased rate of gestational diabetes. Finland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

Having considered the available evidence arising from a recent publication by *Park et al.* (2018), the PRAC agreed that Eli Lilly Nederland B.V. should submit a cumulative review of data on gestational diabetes and related terms in association with olanzapine use during pregnancy.

The PRAC appointed Kimmo Jaakkola as Rapporteur for the signal.

Summary of recommendation(s)

- The originator MAH for olanzapine-containing products should submit to EMA, within 60 days, a cumulative review of the signal, including clinical data from all sources and relevant literature (including the publication from *Park et al.*) and evaluate the biological plausibility for a possible association.
- In addition, the MAH Eli Lilly Nederland B.V. should comment on the risk of gestational diabetes associated with olanzapine use during pregnancy separately in patients with and without known risk factors for gestational diabetes, should evaluate and comment the available data on the post-delivery outcome/resolution of the gestational diabetes cases observed in pregnant women treated with olanzapine and should comment on the potential adverse pregnancy outcomes in olanzapine users diagnosed with gestational diabetes, including any potential effect to the offspring as well as maternal complication.
- The MAH should also discuss the need for any potential amendment to the product information and/ or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Adalimumab – AMGEVITA (CAP), CYLTEZO (CAP), HUMIRA (CAP), IMRALDI (CAP), SOLYMBIC (CAP); infliximab – FLIXABI (CAP), INFLECTRA (CAP), REMICADE (CAP), REMSIMA (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Humira), Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Celltrion Healthcare Hungary Kft. (Remsima), Janssen Biologics B.V. (Remicade), Pfizer Europe MA EEIG (Inflectra), Samsung Bioepis UK Limited (Flixabi, Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of risk of lymphoma in patients with inflammatory bowel disease

EPITT 19121 – Follow-up to April 2018

⁷ Park Y, Hernandez-Diaz S, Bateman BT, et al: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *Am J Psychiatry* 2018; 175: 564–574

Background

For background information, see [PRAC minutes April 2018](#).

The authors of the study presented in the publication by *Lemaitre et al.*⁸ replied to the request for information on the signal of risk of lymphoma in patients with inflammatory bowel disease and the responses were assessed by the Rapporteur.

Discussion

Having considered the responses from the study authors (*Lemaitre et al.*), the PRAC noted that some methodological limitations still remain. In addition, considering that the target patient population treated with combination therapy (i.e. TNF α inhibitors and thiopurines) have a higher use of corticosteroids which indicates more severe disease, the PRAC noted the difficulty to disentangle the effect of combined treatment from the effect of the severity of the disease. Also, considering that in the current product information of both the TNF α inhibitors (i.e. adalimumab, infliximab) and thiopurines the risk of lymphoma is adequately addressed and that the study confirms this previous knowledge, no further actions are deemed warranted at this time apart of routine safety surveillance.

Summary of recommendation(s)

- The PRAC considered that no further actions are deemed warranted at this time apart of routine safety surveillance.

4.3.2. Belimumab – BENLYSTA (CAP)

Applicant(s): Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lupus nephritis

EPITT 19174 – Follow-up to April 2018

Background

For background information, see [PRAC minutes April 2018](#).

The MAH replied to the request for information on the signal of lupus nephritis (LN) and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the cumulative review submitted by the MAH for the signal of lupus nephritis with Benlysta (belimumab) and agreed that further data are needed to reach a conclusion. A subsequent list of questions is to be addressed by the MAH.

Summary of recommendation(s)

- The MAH for Benlysta (belimumab) should submit to EMA, within 30 days, a presentation of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) item that increased in score in study BEL112341⁹ with a clarification if this renal domain

⁸ Lemaitre M, Kirchesner J and al. Association between use of thiopurines or Tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *Jama*. 2017

⁹ A phase 3, multi-center, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab (HGS1006) administered subcutaneously (SC) to subjects with systemic lupus erythematosus (SLE). NCT number: NCT01484496. EudraCT: 2011-003814-18

worsening led to any change in the systemic lupus erythematosus (SLE) treatment for these subjects, a presentation of pooled data from all clinical Benlysta trials (also including study BEL113750¹⁰) with the frequency LN and other preferred terms in renal and urinary disorders MedDRA SOC¹¹, a discussion on whether treating a patient with high disease activity with Benlysta (belimumab) can lead to a false sense of security if it turns out that Benlysta (belimumab) does not protect against development of LN, a summary where cases of de novo occurrence and cases of aggravation of LN are presented separately, a discussion on whether it would be possible to analyse immunoglobulin M/immunoglobulin G (IgM/IgG) isotypes for anti-dsDNA¹² antibodies in stored samples from the pivotal SLE trials and from the ongoing LN study, and a calculation of prevalence and incidence rates, using pooled dataset of clinical trials (completed and ongoing, where possible), in the occurrence of LN events in patients stratified by ethnicity. In addition, the MAH should make every effort to obtain additional data with regards to autoantibody profile, anti-ds-DNA levels and complement levels for these cases.

- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3.3. Direct acting antivirals (DAAV) indicated for the treatment of hepatitis C: Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/SDA/021; dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/SDA/010; elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/SDA/010; glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/SDA/009; ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/SDA/019; ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/SDA/012; sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/SDA/026; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/SDA/010; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/SDA/003

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Exviera, Maviret, Viekirax), Bristol-Myers Squibb Pharma EEIG (Daklinza), Gilead Sciences Ireland UC (Eplusa, Harvoni, Sovaldi, Vosevi), Merck Sharp & Dohme B.V. (Zepatier)

PRAC Rapporteur: Julie Williams

Scope: Signal of dysglycaemia

EPITT 19234 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

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

Discussion

¹⁰ A 52 week study of belimumab versus placebo in the treatment of subjects with systemic lupus erythematosus (SLE) located in Northeast Asia. NCT number: NCT01345253

¹¹ Medical dictionary for regulatory activities – System Organ Class (SOC)

¹² The anti-double stranded DNA (anti-dsDNA) test is used to help diagnose lupus (systemic lupus erythematosus, SLE) in a person who has a positive result on a test for antinuclear antibody (ANA) and has clinical signs and symptoms that suggest lupus

Having considered the available evidence in the literature and EudraVigilance, and the responses from the MAHs, the PRAC agreed that the MAHs for direct-acting antivirals against hepatitis C (Daklinza (daclastavir), Epclusa (sofosbuvir, velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir, sofosbuvir), Maviret (glecaprevir, pibrentasvir), Sovaldi (sofosbuvir), Viekirax (ombitasvir, paritaprevir, ritonavir), Vosevi (sofosbuvir, velpatasvir, voxilaprevir), Zepatier (elbasvir, grazoprevir)) should submit a variation in order to amend the product information to include a special warning and precaution for use in diabetic patients particularly at initiation of a treatment.

Summary of recommendation(s)

- The MAHs of direct-acting antivirals against hepatitis C (Daklinza (daclastavir), Epclusa (sofosbuvir, velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir, sofosbuvir), Maviret (glecaprevir, pibrentasvir), Sovaldi (sofosbuvir), Viekirax (ombitasvir, paritaprevir, ritonavir), Vosevi (sofosbuvir, velpatasvir, voxilaprevir), Zepatier (elbasvir, grazoprevir)) should submit to EMA, within 60 days, a variation to amend the product information¹³.
- In addition, the MAHs should closely monitor cases of hyperglycaemia in PSURs.

For the full PRAC recommendation, see [EMA/PRAC/689235/2018](#) published on 29/10/2018 on the EMA website.

4.3.4. Dolutegravir – TIVICAY (CAP) – EMEA/H/C/002753/SDA/009; abacavir sulfate, dolutegravir sodium, lamivudine – TRIUMEQ (CAP); dolutegravir, rilpivirine – JULUCA (CAP)

Applicant(s): ViiV Healthcare B.V. (Tivicay), ViiV Healthcare UK Limited (Juluca, Triumeq)

PRAC Rapporteur: Julie Williams

Scope: Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women

EPITT 19244 – Follow-up to June 2018

Background

For background information, see [PRAC minutes June 2018](#).

The MAH replied to the request for information on the evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available evidence from the preliminary data of an observational study on birth outcomes in HIV-infected women – the Tsepamo study¹⁴ conducted in Botswana, as well as the additional data submitted by the MAH in relation to the safety of use of dolutegravir during pregnancy (from clinical trials, post-marketing experience and literature). The PRAC confirmed its [precautionary advice](#), issued earlier this year, that women of child bearing potential should use effective contraception while taking dolutegravir. In addition, women should undergo pregnancy testing before starting treatment and the

¹³ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

¹⁴ Observational study capturing birth outcomes data at 8 government hospitals throughout Botswana (~45% of all deliveries) starting August 2014

medicine should not be used during the first trimester of pregnancy unless there is no alternative. The PRAC also agreed updates relating to recommendations around use during the second and third trimester of pregnancy. The PRAC agreed that the MAH of dolutegravir containing products (ViiV Healthcare) should submit a variation in order to update the product information accordingly. Of note, when more complete data from the Tsepamo study, as well as data from other sources (including the non-clinical studies) become available, the MAH should consider taking the appropriate steps, including submitting further variations as applicable, in order to fully inform the present understanding about the risk of neural tube defects and the implications of the use of dolutegravir during pregnancy. Alongside the update of the product information the MAH should amend the RMP to include the neural tube defects as a potential risk, to upgrade the review of data from the Antiretroviral Pregnancy Registry (APR) in the pharmacovigilance plan, and to add the DOLOMITE programme¹⁵ to the pharmacovigilance plan. Moreover, the MAH should closely monitor pregnancy outcomes in future PSURs. The PRAC agreed that the views of the Safety Working Party ([SWP](#)) should be sought on further non-clinical studies.

Summary of recommendation(s)

- The MAH for dolutegravir-containing medicinal products should submit to the EMA, within 30 days, a variation to amend the product information¹⁶ to include relevant information for the use of dolutegravir in women of childbearing potential as well as during pregnancy. The RMP should be amended accordingly.
- The MAH for dolutegravir-containing medicinal products should closely monitor pregnancy outcomes in future PSURs.
- In addition, the MAH for dolutegravir-containing medicinal products should, in the next PSUR, and/or following PSURs, as applicable and as soon as the information becomes available, provide updates on the results of the investigations on dolutegravir, including information on neural tube development, the possible mechanisms and any risk factors including whether individuals with a MC4¹⁷ mutation might have an increased sensitivity to dolutegravir. The MAH should also provide updates from relevant ongoing studies including the Brazil Pregnancy Cohort and provide final results of the Tsepamo study.
- Finally, the PRAC agreed that the views of the Safety Working Party ([SWP](#)) should be sought on further non-clinical studies for consideration at the PRAC meeting in January 2019.

For the full PRAC recommendation, see [EMA/PRAC/689235/2018](#) published on 29/10/2018 on the EMA website.

4.3.5. Hormonal contraceptives:

Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol¹⁸ (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestrel acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene¹⁹ (NAP); ethinylestradiol, gestodene²⁰ (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP;

¹⁵ The dolutegravir in pregnancy programme set up to provide comprehensive data on pharmacokinetics, usage, safety and effectiveness of dolutegravir in pregnancy in real world settings in Europe

¹⁶ Update of SmPC section 4.6. The package leaflet is to be updated accordingly

¹⁷ Melanocortin 4

ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol²¹ (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

Applicant(s): Teva B.V (Zoely), Janssen-Cilag International NV (Evra), various

PRAC Rapporteur: Menno van der Elst

Scope: Signal related to a known association between hormonal contraceptives and a small increase in breast cancer following a recent publication

EPITT 19143 – Follow-up to July 2018

Background

For background information, see [PRAC minutes July 2018](#).

The MAH replied to the request for information on the signal related to a known association between hormonal contraceptives and a small increase in breast cancer following a recent publication and the responses were assessed by the Rapporteur.

Discussion

Having considered the study by *Mørch et al.*, 2017²² in the context of the available evidence, which includes thirteen single studies and five systematic reviews and meta-analyses, the PRAC agreed that the study by *Mørch et al.* confirms the known risk of breast cancer in association with combined hormonal contraceptives, as reflected in the European product information. However, the total body of evidence is insufficient to clearly establish an increased risk of breast cancer associated with less than 5 years of hormonal contraceptives use. The data on oral progestogen-only products presented in the study by *Mørch et al.* are also too limited to draw robust conclusions.

No update to the product information is deemed warranted at this stage. However, the MAHs for hormonal contraceptive-containing products should closely monitor the risk of breast cancer in association with the duration of use, as part of routine safety surveillance.

Summary of recommendation(s)

- The PRAC considered that no update to the product information is deemed warranted at this stage.
- The MAHs for hormonal contraceptive-containing products should closely monitor the risk of breast cancer in association with the duration of use, as part of routine safety surveillance.

4.3.6. Hormonal contraceptives:

Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogesterone acetate (NAP); conjugated estrogens, norgestrel (NAP);

¹⁸ Contraception indication

¹⁹ All route of administrations except transdermal

²⁰ Transdermal application

²¹ Combination pack

²² Mørch, L. S., Skovlund, C. W., Hannaford, P. C., Iversen, L., Fielding, S. and Lidegaard, O. 2017. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*, 377, 2228-2239

cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol²³ (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, norgestrel acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol (17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene²⁴ (NAP); ethinylestradiol, gestodene²⁵ (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol²⁶ (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); norgestrel (NAP); norgestrel acetate, estradiol – ZOELY (CAP); norelgestromin, ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP)

Applicant(s): Teva B.V (Zoely), Janssen-Cilag International NV (Evra), various

PRAC Rapporteur: Doris Stenver

Scope: Signal of suicidality with hormonal contraceptives following a recent publication

EPITT 19144 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

The MAH replied to the request for information on the signal of suicidality with hormonal contraceptives following a recent publication and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered that the limitations of the available data did not allow to clearly establish whether there is an increased risk of suicidal thoughts and behaviour associated with the use of hormonal contraceptives. However, it was recognised that depressed mood and depression are known to occur in association with the use of hormonal contraceptives. Depression is serious and can sometimes lead to suicidal thoughts and it was considered important to reflect the potential severity of the condition in the product information for hormonal contraceptives. Therefore, the PRAC agreed that the MAHs for the hormonal contraceptive products are to submit a variation in order to amend the product information to include special warnings and precautions for use on mood changes, including that depression can be serious and is a well-known risk factor for suicidal behaviour and suicide and women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Summary of recommendation(s)

²³ Contraception indication

²⁴ All route of administrations except transdermal

²⁵ Transdermal application

²⁶ Combination pack

- The MAHs for hormonal contraceptive-containing products should submit to EMA and the EU National Competent Authorities as appropriate, within 60 days, a variation to update the product information²⁷.

For the full PRAC recommendation, see [EMA/PRAC/689235/2018](#) published on 29/10/2018 on the EMA website.

4.3.7. [Oxybutynin – KENTERA \(CAP\), NAP; carbamazepine \(NAP\)](#)

Applicant(s): Nicobrand Limited (Kentera), various

PRAC Rapporteur: Laurence de Fays

Scope: Signal on drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations

EPITT 19233 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

The MAHs replied to the request for information on the signal of drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance, published literature, clinical and in vitro studies and data mining of FAERS²⁸ and VigiBase²⁹, the PRAC agreed that an interaction between oxybutynin and carbamazepine cannot be confirmed. The weighted cumulative evidence is not sufficiently strong at this stage to suggest a clinically relevant pharmacokinetic (PK) interaction between oxybutynin and carbamazepine leading to carbamazepine blood level decrease or increase or leading to occurrence of seizures. The PRAC agreed that no further action is deemed warranted at this stage. However, the MAHs of oxybutynin-containing products and carbamazepine-containing products should continue to monitor these events as part of routine safety surveillance.

Summary of recommendation(s)

- The PRAC agreed that no further action is deemed warranted at this stage.
- The MAHs of oxybutynin-containing products and carbamazepine-containing products should continue to monitor these events as part of routine safety surveillance.

4.3.8. [Teriflunomide – AUBAGIO \(CAP\) - EMEA/H/C/002514/SDA/004](#)

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of dyslipidaemia

²⁷ Update of SmPC section 4.4. The package leaflet is to be updated accordingly

²⁸ FDA Adverse Event Reporting System

²⁹ Uppsala Monitoring Centre – World Health Organization global database of individual case safety reports (ICSRs)

EPITT 19227 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

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

Discussion

Having considered the available evidence in EudraVigilance, the literature, clinical trials and the cumulative review provided by the MAH of Aubagio (teriflunomide), Sanofi-aventis groupe, the PRAC agreed that the MAH of Aubagio (teriflunomide) should submit a variation in order to amend the product information to include dyslipidaemia as an undesirable effect with a frequency 'not known'.

Summary of recommendation(s)

- The MAH for Aubagio (teriflunomide) should submit to EMA, within 60 days, a variation to amend the product information³⁰.

For the full PRAC recommendation, see [EMA/PRAC/689235/2018](#) published on 29/10/2018 on the EMA website.

4.3.9. Trastuzumab – HERCEPTIN (CAP) - EMEA/H/C/000278/SDA/101, HERZUMA (CAP) - EMEA/H/C/002575/SDA/002, ONTRUZANT (CAP) - EMEA/H/C/004323/SDA/003; trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/SDA/020; pertuzumab – PERJETA (CAP) - EMEA/H/C/002547/SDA/013

Applicant(s): Celltrion Healthcare Hungary Kft. (Herzuma), Roche Registration GmbH (Herceptin, Kadcyla, Perjeta), Samsung Bioepis UK Limited (SBUK) (Ontruzant)

PRAC Rapporteur: Doris Stenver

Scope: Signal of multiple sclerosis relapse

EPITT 19208 – Follow-up to May 2018

Background

For background information, see [PRAC minutes May 2018](#).

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

Discussion

Having considered the available evidence from EudraVigilance, literature and pre-clinical and clinical data, the PRAC agreed that no further action is deemed warranted at this stage. However Roche Registration GmbH, the MAH for Herceptin (trastuzumab), Kadcyla (trastuzumab emtansine) and Perjeta (pertuzumab), Celltrion Healthcare Hungary Kft., the MAH for Herzuma (trastuzumab) and Samsung Bioepis UK Limited, the MAH for Ontruzant (trastuzumab) respectively, should closely monitor in PSURs incidence and progression of multiple sclerosis.

³⁰ Update of SmPC section 4.8. The package leaflet is to be updated accordingly

Summary of recommendation(s)

- The PRAC considered that no further action is deemed warranted at this stage.
- The MAHs for Herceptin (trastuzumab), Herzuma (trastuzumab), Ontruzant (trastuzumab), Kadcyła (trastuzumab emtansine) and Perjeta (pertuzumab), should closely monitor in PSURs incidence and progression of multiple sclerosis.

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 (<https://www.ema.europa.eu/en/committees/chmp/chmp-agendas-minutes-highlights>).

See also Annex I 15.1.

5.1.1. Botulinum toxin type A - EMEA/H/C/004587

Scope: Temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows

5.1.2. Dapivirine - Art 58³¹ - EMEA/H/W/002168

Scope: Reduction of the risk of human immunodeficiency virus-1 (HIV-1) infection via vaginal intercourse in sexually active HIV-uninfected women

5.1.3. Lorlatinib - EMEA/H/C/004646

Scope: Treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

5.1.4. Lusutrombopag - EMEA/H/C/004720

Scope: Treatment of thrombocytopenia

5.1.5. Treosulfan - EMEA/H/C/004751, Orphan

Applicant: Medac Gesellschaft für klinische Spezialpräparate

Scope: Conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT)

³¹ 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)

5.1.6. Zanamivir - EMEA/H/C/004102

Scope: Treatment of influenza A or B virus infection

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

See also Annex I 15.2.

5.2.1. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/II/0148

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Update of Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' to implement information on education material proposal to address the incorrect self-administration of Aranesp (darbepoetin alfa) via the SureClick pre-filled pen and associated dosing errors. The RMP (version 9.1) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template)

Background

Darbepoetin alfa is a type of recombinant erythropoietin indicated, as Aranesp, for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients as well as for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

The PRAC is evaluating a type II variation procedure for Aranesp, a centrally authorised medicine containing darbepoetin alfa, to implement information on proposed education material key elements in order to address the incorrect self-administration of Aranesp (darbepoetin alfa) via the SureClick pre-filled pen and associated dosing errors as well as to further implement the outcome PRAC adopted in January 2017 for a 'signal of incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions' and the requested variation (EMEA/H/C/000332/II/0143) for which PRAC provided CHMP with advice in September 2017. For further background, see [PRAC minutes January 2017](#) and [PRAC minutes September 2017 \(29 August-1 September\)](#). The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Aranesp (darbepoetin alfa) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 9.1 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The final educational material should be agreed with the national competent authority (NCAs) where the pre-filled pen is marketed. Healthcare professionals (HCPs) prescribing Aranesp (darbepoetin alfa) pre-filled pen should be provided educational materials with the aim to facilitate training patients on the correct self-administration of Aranesp. The HCP training checklist and the demonstration device (training poster/video) should be amended with agreed key elements. As a consequence, Annex-

D should be updated. Finally, the MAH should update the summary of safety concerns as advised by PRAC.

5.2.2. Panobinostat - FARYDAK (CAP) - EMEA/H/C/003725/II/0013, Orphan

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.0) in order to remove the commitment to conduct a study LBH589D2408 (listed as a category 3 study in the RMP): a non-interventional PASS of panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events

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.

The PRAC is evaluating a type II variation procedure for Farydak, a centrally authorised medicine containing panobinostat, to update the RMP in order to remove the commitment to conduct study LBH589D2408, a non-interventional PASS³² (listed as a category 3 study in the RMP) exploring panobinostat use in relapsed or relapsed/refractory multiple myeloma patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent in a real-world setting according to the current EU prescribing information and document adherence to dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

Summary of advice

- The RMP for Farydak (panobinostat) in the context of the variation procedure under evaluation could be considered acceptable provided that an update to RMP version 5.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered the MAH's proposal to remove the PASS from the RMP as it is no longer feasible due to recruitment issues but to retain potential risk of medication errors and compliance card. The PRAC agreed to a request of a detailed review of the data from the patients recruited in the study to date, e.g. baseline characteristics, and details of any adverse effects including any possible reported medication errors. In addition, the MAH should provide yearly breakdown of exposure per EU Member State from the time of launch to date. The MAH should also discuss alternative options to evaluate the effectiveness of the compliance card and to develop a follow-up questionnaire for all post-marketing reports of medication errors, to support causality assessment. Finally,

³² Protocol agreed by PRAC in September 2016

the MAH is requested to re-assess available data from all sources for all events of interest with a view to strengthen the current risk minimisation measures and/or revise the list of safety concerns in line with revision 2 of GVP module V on 'risk management systems'.

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

See also Annex I 15.3.

5.3.1. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/WS1344/0025; FORXIGA (CAP) - EMEA/H/C/002322/WS1344/0044

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Extension of indication to include the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control, for Forxiga and Edistride (dapagliflozin). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 16) are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the SmPC and package leaflet

Background

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated, as Edistride and Forxiga, in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. It is also indicated as add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The CHMP is evaluating a worksharing application consisting of an extension of the therapeutic indication for Edistride and Forxiga, centrally authorised products containing dapagliflozin, to include a new indication for the treatment of insufficiently controlled type 1 diabetes mellitus (T1DM) as an adjunct to insulin, when insulin does not provide adequate glycaemic control. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication. For further background, see [PRAC minutes May 2018](#).

Summary of advice

- The RMP for Edistride and Forxiga (dapagliflozin) in the context of the worksharing variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 16 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC raised concerns in relation to the high rates of diabetic ketoacidosis (DKA) which occurred in the clinical trial setting, in spite of rigorous additional risk minimisation activities in this setting. Therefore, the PRAC supported the request for the MAH to provide further evidence on the effectiveness of the proposed measures to minimise the risk of DKA in the real world setting. With regard to the proposed study to assess the effectiveness of additional RMMs, the MAH should provide a study synopsis

and details on proposed timelines. Furthermore, the MAH should provide a more detailed proposal for the educational material/patient alert card.

5.3.2. Omalizumab - XOLAIR (CAP) - EMEA/H/C/000606/II/0092

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2, 4.4, 4.6 and 6.6 of the SmPC for Xolair (omalizumab) solution for injection in pre-filled syringe (PFS) to allow for home use in severe allergic asthma and chronic spontaneous urticaria. Consequential updates are applied to the SmPC for powder and solvent for solution for injection. Artwork for the outer box, the blister and the syringe label for Xolair (omalizumab) solution for injection in PFS are updated to ensure that patients/lay caregiver can more easily distinguish the two strengths of Xolair PFS. The package leaflet, labelling and the RMP (version 13) are updated accordingly

Background

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE) preventing from binding of IgE to FcεRI³³ receptors. It is indicated, as Xolair, as add-on therapy in adults and adolescents of 12 years of age and older to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. It is also indicated as add-on therapy in children of 6 years to <12 years of age to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

The CHMP is evaluating a variation consisting of an extension of the therapeutic indication for Xolair, a centrally authorised product containing omalizumab, to allow the option of home use of the solution for injection in pre-filled syringe by self-administration or lay caregiver in the case of severe allergic asthma and chronic spontaneous urticaria. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP for Xolair (omalizumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 13 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC considered that the MAH should be requested to propose routine pharmacovigilance activities to characterise the incidence of anaphylactic reactions in home use patients as well as whether the patients received adequate training and sufficient information prior to home use. In addition, the MAH should discuss in details

³³ High-affinity IgE receptor, also known as Fc epsilon RI

the way patient and/or caregiver ability to self-inject the medicinal product will be assessed by healthcare professionals (HCPs) prior to and during home use to ensure the correct injection technique is used.

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. Apremilast - OTEZLA (CAP) - PSUSA/00010338/201803

Applicant: Celgene Europe BV

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

Background

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor indicated, as Otezla, for the treatment alone or in combination with disease modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. It is also indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Otezla, a centrally authorised medicine containing apremilast 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 Otezla (apremilast) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add angioedema as an undesirable effect with a frequency 'not known' and urticaria with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should provide detailed reviews of cases of tubulointerstitial diseases, of cases of severe cutaneous adverse reactions (SCARs) as well as of cases of hallucination/visual hallucination. The MAH should propose to update the product information as warranted. In addition, the MAH should discuss the hypothesis described by *Kalik et al, 2017*³⁵ with regards to the mechanism apremilast could potentially have a role in the development of vasculitis.

³⁴ 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

³⁵ Kalik JA, Friedman H, Bechtel MA, Gru AA, Kaffenberger BH. Purpura annularis telangiectodes of Majocchi associated with the initiation and rechallenge of apremilast for psoriasis vulgaris. *JAMA dermatology* 2017 Aug 9

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. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201803

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

Background

Naloxegol is a pegylated derivative of the mu-opioid receptor antagonist naloxone indicated, as Moventig, for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Moventig, a centrally authorised medicine containing naloxegol 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 Moventig (naloxegol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include that the use of naloxegol with another opioid antagonist should be avoided due to the potential for an additive effect of opioid receptor antagonism and an increased risk of opioid withdrawal. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.
- In the next PSUR, the MAH should provide detailed reviews of cases reporting 'drug ineffective' and of 'gastrointestinal related adverse events'. In addition, the MAH should provide a cumulative analysis of the risk of 'interference with opioid mediated analgesia'. Finally, the MAH should discuss the need to amend the current risk minimisation measures on gastrointestinal perforation to mitigate this risk as warranted.

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

6.1.3. Pembrolizumab - KEYTRUDA (CAP) - PSUSA/00010403/201803

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 which binds to the programmed cell death-1 (PD-1) receptor. It is indicated, as Keytruda, for the treatment of advanced

³⁶ 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

(unresectable or metastatic) melanoma in adults, for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express programmed death-ligand 1 (PD-L1) with a $\geq 50\%$ tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations, for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen as well as for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. In addition, it is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy as well as for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

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 add 'Vogt-Koyanagi-Harada syndrome' and 'pure red cell aplasia' as new undesirable effects with a frequency 'rare' and to add 'including exacerbation' to the existing undesirable effect of myasthenia gravis. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.
- In the next PSUR, the MAH should discuss new cases of cholangitis (sclerosing).

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. Velaglucerase alfa - VPRIV (CAP) - PSUSA/00003103/201802

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Velaglucerase alfa is a glycoprotein indicated, as Vpriv, for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

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

Summary of recommendation(s) and conclusions

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vpriv (velaglucerase alfa) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to the EMA, within 90 days, detailed reviews of cases of 'medication errors' and of cases where 'vomiting' is reported. In addition, a cumulative review of cases of 'blurred vision' should be provided.
- In the next PSUR, the MAH should provide a detailed review of hypersensitivity reactions including hypersensitivity reactions defined as infusion related reactions (IRR).

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

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

See also Annex I 16.2.

6.2.1. Estradiol, nomegestrol acetate - ZOELY (CAP); NAP - PSUSA/00002182/201801

Applicants: Teva B.V. (Zoely), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

Background

Estradiol is an oestrogen and nomegestrol acetate a progestogen. Estradiol/nomegestrol acetate in combination is indicated for oral contraception and for menopausal hormone replacement therapy (HRT) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zoely, a centrally authorised medicine containing estradiol/nomegestrol acetate, and nationally authorised medicines containing estradiol/nomegestrol acetate and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of estradiol/nomegestrol acetate-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAH for Zoely (estradiol/nomegestrol acetate) should submit to EMA, within 90 days, a detailed review of cases of meningioma associated with estradiol/nomegestrol use including a thorough discussion on whether the individual dose of each component and interactions between oestrogens and progestogens could limit the extrapolation from nomegestrol monocomponent to Zoely (estradiol/nomegestrol acetate) in relation to this risk. Moreover, based on the information provided, the MAH should discuss the need to update the product information if warranted.

- In the next PSUR, the MAHs should also closely monitor the risk of meningioma.

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

6.2.2. Pemetrexed - ALIMTA (CAP); ARMISARTE (CAP); NAP - PSUSA/00002330/201802

Applicants: Actavis Group PTC ehf (Armisarte), Eli Lilly Nederland B.V. (Alimta), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Pemetrexed is a multi-targeted anti-cancer antifolate agent indicated as second-line monotherapy or first-line with cisplatin in the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) and as maintenance monotherapy in patients whose disease has not progressed after platinum-based first-line chemotherapy. Pemetrexed is also used with cisplatin in the first-line treatment of unresectable malignant pleural mesothelioma.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of pemetrexed-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include 'hyperpigmentation' as an undesirable effect with a frequency 'common'. In addition, the undesirable effect section should be further updated to add 'infectious and non-infectious disorders of the dermis, the hypodermis and/or the subcutaneous tissue (e.g. acute bacterial dermo-hypodermatitis, pseudocellulitis and dermatitis)' with a frequency 'not known'. Therefore, the current terms of the marketing authorisations should be varied³⁸.
- In the next PSUR, the MAHs should closely monitor the risk of potential interaction between lansoprazole/proton pump inhibitors (PPI) and pemetrexed, the risk of cardiomyopathy and should include a detailed review of cases of 'drug reaction with eosinophilia and systemic symptoms (DRESS)'. In addition, the MAH Eli Lilly should present information on the rate of patients who received an appropriate prophylaxis with folic acid and vitamin B12 since 2007 when the follow-up of such cases and information started to be sent to healthcare professionals (HCPs). Eli Lilly is requested to propose risk minimisation measures and to consider an update of the RMP as applicable.
- The PRAC considered that some of the safety concerns of the RMP are already sufficiently characterised, have no additional pharmacovigilance activities or risk

³⁸ 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

minimisation measures, and information in the product information is sufficient to reduce these risks and therefore can be deleted. The affected safety concerns include 'non-compliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities', 'bone marrow suppression', 'gastrointestinal disorders', 'renal disorders', 'sepsis', 'bullous skin reaction, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)', 'interstitial pneumonitis', 'radiation pneumonitis' and 'radiation recall'. The PRAC also concurred that the potential risk of 'medication error' should be applied to all pemetrexed-containing products. Further consideration is to be given at the level of the CHMP and CMDh.

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

6.2.3. Voriconazole - VFEND (CAP); NAP - PSUSA/00003127/201802

Applicant: Pfizer Limited, various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

Background

Voriconazole is a triazole antifungal agent indicated in adults and children aged 2 years and above for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. and prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

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

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of voriconazole-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to add 'drug reaction with eosinophilia and systemic symptoms (DRESS)' as an undesirable effect with a frequency 'rare' and to revise the existing warning on exfoliative cutaneous reactions and severe cutaneous adverse reactions (SCARs) to add DRESS. Therefore, the current terms of the marketing authorisations should be varied³⁹.

The frequency of PSUR submission should be revised from yearly to three-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.

³⁹ 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

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

See also Annex I 16.3.

6.3.1. Bilastine (NAP) - PSUSA/00003163/201803

Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

Background

Bilastine is a long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity indicated in the symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing bilastine 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 bilastine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add 'vomiting' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁰.

The frequency of PSUR submission should be revised from yearly to three-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.

6.3.2. Cilazapril (NAP); cilazapril, hydrochlorothiazide (NAP) - PSUSA/00000749/201802

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Cilazapril is a long-acting angiotensin-converting enzyme (ACE) inhibitor and hydrochlorothiazide a thiazide-diuretic agent. Cilazapril alone is indicated for the treatment of hypertension and chronic heart failure (CHF). In combination, cilazapril/hydrochlorothiazide is indicated in the treatment of hypertension in patients who have been stabilised on the individual components given in the same proportions.

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

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing cilazapril and cilazapril/hydrochlorothiazide 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 cilazapril- and cilazapril/hydrochlorothiazide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication and a warning regarding concomitant use with sacubitril/valsartan due to the increased risk of angioedema as well as to add a warning on interaction information regarding concomitant use with racecadotril, mTOR⁴¹ inhibitors and vildagliptin as it may lead to an increased risk of angioedema. In addition, a warning is added regarding interaction with trimethoprim, trimethoprim/sulfamethoxazole, ciclosporin and heparin as it can cause hyperkalaemia. Serum potassium level should be monitored. Therefore, the current terms of the marketing authorisation(s) should be varied⁴².
- In the next PSUR, MAHs should provide a cumulative review of the potential association of cilazapril, hydrochlorothiazide and myocarditis and pericarditis following the publication by *Haddad et al.*⁴³. In addition, MAHs should provide a cumulative review of the potential association of cilazapril, hydrochlorothiazide and hearing disorders following the published case series by *Belai et al.*⁴⁴.
- The PRAC considered that interactions with sacubitril/valsartan, racecadotril and vildagliptin resulting in an increased risk of angioedema, and that interactions with trimethoprim, ciclosporin, and heparin resulting in an increased risk of hyperkalaemia are also relevant for inclusion in the product information for other ACE inhibitors, as the available evidence and likely mechanisms indicate that these pharmacodynamic interactions are class effects of ACE inhibitors. Further consideration is to be given at the level of the CMDh.

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

6.3.3. Ciprofloxacin⁴⁵ (NAP) - PSUSA/00000775/201801

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

Background

⁴¹ Mammalian target of rapamycin

⁴² Update of SmPC sections 4.3, 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

⁴³ Haddad TM, Nawaz, MS, Abuzaid AS et al. Probable hydrochlorothiazide-induced myopericarditis: first case reported. *Case Rep Med.* 2015; 2015: 319086

⁴⁴ Belai N, Gebrehiwet S, Fitsum Y et al. Hydrochlorothiazide and risk of hearing disorder: a case series. *J Med Case Rep.* 2018; 12: 135

⁴⁵ Systemic use only

Ciprofloxacin is a selective inhibitor of bacterial type II and type IV topoisomerases, belonging to the chemical class of fluoroquinolones (FQ). It is indicated for the treatment of uncomplicated and complicated infections caused by ciprofloxacin susceptible pathogens: infections of the respiratory tract, infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis), especially if these are caused by Gram-negative organisms including *Pseudomonas aeruginosa* or by *staphylococci*. It is also indicated in the treatment of infections of the eyes, infections of the kidneys and/or the efferent urinary tract, infections of the genital organs, including adnexitis, gonorrhoea, prostatitis, infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis), infections of the skin and soft tissue, infections of the bones and joints, sepsis, infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or who have neutropenia), selective intestinal decontamination (SID) in immunosuppressed patients and for the prophylaxis of invasive infections due to *Neisseria meningitides*.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ciprofloxacin for systemic use 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 ciprofloxacin-containing medicinal products for systemic use in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to revise the warning on dysglycaemia to add information on hypoglycaemic coma and to add 'reactions syndrome of inappropriate secretion of antidiuretic hormone (SIADH)' as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁶. This recommendation is without prejudice to the final conclusions of the referral procedure under Article 31 of Directive 2001/83/EC for fluoroquinolones and quinolones for systemic and inhalation use (EMA/H/A-31/1452). See under 3.3.1.
- In the next PSUR, the MAH should closely monitor cases of acute respiratory distress syndrome (ARDS), optic neuritis/optic neuropathy, atrial arrhythmia, interaction with nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of seizures/convulsion as well as cases of hypoglycaemic coma.
- The PRAC considered that a warning on hypoglycaemic coma is relevant for inclusion in the product information of the whole class of fluoroquinolones. Further consideration is to be given at the level of the CMDh.

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

6.3.4. Lorazepam (NAP) - PSUSA/00001909/201801

Applicant(s): various

⁴⁶ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

Background

Lorazepam is a benzodiazepine (BZD) indicated for the short-term management of anxiety disorders, insomnia, alcohol withdrawal and surgical pre-medication. It is also indicated for pre-operative medication or pre-medication for uncomfortable or prolonged investigations (e.g., bronchoscopy, arteriography, endoscopy), for the treatment of acute anxiety states, acute excitement or acute mania and for the control of status epilepticus.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lorazepam 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 lorazepam-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a warning on the increased risk of falls in elderly patients due to the risk of sedation and/or musculoskeletal weakness. As a consequence, elderly patients should be given a reduced dose. Therefore, the current terms of the marketing authorisation(s) should be varied⁴⁷.
- In the next PSUR, MAHs should provide detailed reviews on benzodiazepine drug abuse, drug misuse, drug dependence, suicide and overdose in patients based on the publications by *Bachhuber MA et al*⁴⁸, *Masmoudi R et al*⁴⁹, *Peritogiannis V et al*⁵⁰, *Rubio González V et al*⁵¹, *Téllez-Lapeira JM et al*⁵² and *Schmitz A et al*⁵³. MAHs are requested to consider whether specific additional risk minimisation actions can be initiated to reduce drug abuse, drug misuse, drug dependence, suicide and overdose in patients. In addition, MAHs should include a detailed review, including the publication by *Nakafero G et al*⁵⁴ on the association between benzodiazepines and influenza-like illness-related pneumonia and mortality. Based on the review, MAHs should consider updating the product information as warranted. Finally, the MAHs should keep cases reporting 'using during pregnancy' and 'exposure to neonates' under close monitoring.

⁴⁷ Update of SmPC sections 4.2 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

⁴⁸ Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. *Am J Public Health*. 2016 Apr;106(4):686-8

⁴⁹ Dependence on lorazepam in patients consulting in psychiatry. Masmoudi R, Feki I, Ben Touhemi D, Sellami R, Masmoudi J. *European Neuropsychopharmacology*. 2016;26:685

⁵⁰ Long-term benzodiazepine treatment in patients with psychotic disorders attending a mental health service in rural Greece. Peritogiannis V, Manthopoulou T, Mavreas V. *J Neurosci Rural Pract*. 2016 Dec;7(Suppl 1):S26-S30

⁵¹ Hospital emergencies associated with the consumption of hypnotics and sedatives, 2009-2013, Castilla y León, Spain. [Article in Spanish]. Rubio González V, Redondo Martín S, Ruíz López Del Prado G, Muñoz Moreno MF, Velázquez Miranda A. *Rev Esp Salud Publica*. 2016 Oct 24;90:e1-e12

⁵² Determining factors for the use of anxiolytic and hypnotic drugs in the elderly. [Article in Spanish]. Téllez-Lapeira JM, López-Torres Hidalgo J, Gálvez-Alcaraz L, Párraga-Martínez I, Boix-Gras C, García-Ruiz A. *Rev Esp Geriatr Gerontol*. 2017 Jan - Feb;52(1):31-34

⁵³ Benzodiazepine use, misuse, and abuse: a review. Schmitz A. *Ment Health Clin*. 2016 May 6;6(3):120-126

⁵⁴ The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data. Nakafero G, Sanders RD, Nguyen-Van-Tam JS, Myles PR. *Pharmacoepidemiol Drug Saf*. 2016 Nov;25(11):1263-1273

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

6.3.5. Nomegestrol (NAP) - PSUSA/00002181/201801

Applicant(s): various

PRAC Lead: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

Background

Nomegestrol is a progestogen structurally related to progesterone indicated in the treatment of menstrual disorders in pre-menopausal women (premenstrual syndrome, oligomenorrhoea, primary dysmenorrhoea, mastodynia, polymenorrhoea, amenorrhoea, menorrhagia, prolonged menstrual cycle, genital bleeding) and as a hormone replacement therapy (HRT) in postmenopausal women.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing nomegestrol 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 nomegestrol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to add a contraindication for the presence or history of meningioma, a warning in this respect and recommendation to discontinue treatment if meningioma is diagnosed and to add 'meningioma' as an undesirable effect with a frequency 'very rare'. Therefore, the current terms of the marketing authorisation(s) should be varied⁵⁵.

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

6.4.1. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/LEG 038

Applicant: Bayer AG

PRAC Rapporteur: Adrien Inoubli

Scope: Review of non-clinical and clinical data on pregnancy, including all cases reported from clinical trials, post-marketing experience and literature, as requested in the conclusions of PSUSA/00001724/201709 adopted in May 2018

Background

⁵⁵ Update of SmPC sections 4.3, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

Iloprost is a synthetic prostacyclin analogue indicated, as Ventavis, for the treatment of adult patients with primary pulmonary hypertension, classified as NYHA⁵⁶ functional class III, to improve exercise capacity and symptoms.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit all available data on pregnancy (for background, see [PRAC minutes May 2018](#)). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- Based on the submitted data and review, the PRAC considered that the MAH should submit to EMA, within 60 days, a variation⁵⁷ to add a warning on women of child-bearing potential to ensure they use effective contraceptive measures during treatment with Ventavis (iloprost). In addition, women with pulmonary hypertension (PH) should avoid pregnancy as it may lead to life-threatening exacerbation of the disease.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁵⁸

See also Annex I 17.1.

7.1.1. Umeclidinium bromide – INCRUSE ELLIPTA (CAP), ROLUFTA ELLIPTA (CAP); umeclidinium bromide, vilanterol – ANORO ELLIPTA (CAP), LAVENTAIR ELLIPTA (CAP) - EMEA/H/C/PSA/S/0032

Applicants: Glaxo Group Ltd (Anoro Ellipta, Incruse Ellipta, Laventair Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

PRAC Rapporteur: Amelia Cupelli

Scope: Amendment to a protocol initially endorsed by PRAC in March 2015 (EMEA/H/C/PSP/J/003.1) for study 201038: a post-authorisation safety (PAS) observational cohort study to quantify the incidence of selected cardiovascular and cerebrovascular

Background

Umeclidinium bromide is a long acting muscarinic receptor antagonist and vilanterol a selective long-acting, beta₂-adrenergic receptor agonist (beta₂-adrenergic agonist). Umeclidinium bromide is indicated alone as Incruse Ellipta and Rolufta Ellipta, and in combination with vilanterol as Anoro Ellipta and Laventair Ellipta as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D of the marketing authorisation\(s\)](#)) a post-authorisation safety (PAS) observational cohort study has to be conducted to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in COPD patients with these products compared with tiotropium. A protocol for the study was submitted by the MAH and endorsed by PRAC in March 2015 (see [PRAC minutes November](#)

⁵⁶ New York Heart Association

⁵⁷ Update of SmPC section 4.6. The package leaflet is to be updated accordingly

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

[2014](#), [PRAC minutes March 2015](#) and [PRAC minutes October 2015](#) for further background). An amended protocol version 1 was submitted by the MAH on 23 July 2018 and was assessed by the Rapporteur.

Endorsement/Refusal of the protocol

- The PRAC, having considered the amended protocol version 1 in accordance with Article 107o of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal products, as the Committee considered that that the proposed revised design of the study did not fulfil the study objectives.
- The PRAC noted the substantially lower number of events observed that would require an increased estimate of participants necessary for a comparative analysis and therefore would impact on feasibility and timelines concluding on a non-realistic probability to deliver informative evidence in a reasonable time window. Consequently, the PRAC recommended setting up an alternative study design that would include as primary objective the comparison of the incidence rates and hazard ratios of the various events of interest in the 3 arms of the study. Data analysis performed for the study should be thoroughly revised taking into account the request of performing a comparative analysis among treatment groups. The duration of the study, milestones and sample size should be set in accordance with the revised objectives of the study.
- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 day-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁵⁹

See Annex I 17.2.

7.3. Results of PASS imposed in the marketing authorisation(s)⁶⁰

See also Annex I 17.3.

7.3.1. Amino acid combinations, glucose, triglyceride combinations, with or without electrolytes, mineral compounds⁶¹ (NAP) - EMEA/H/N/PSR/S/0017

Applicant: Baxter Healthcare Limited (Numeta)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to PSR/S/0017 [PASS results for a multicentre, non-interventional, uncontrolled, open-label, observational study in children (up to age 24 months) to generate descriptive data for serum magnesium (Mg) levels in full-term, newborn infants and children up to 24 months of age following dosing with Numeta G16%E; to observe the following parameters in subjects who receive parenteral nutrition (PN) with Numeta G16%E: 1) actual infused Numeta G16%E intake (mL/kg/day); 2) actual nutritional intake (total calories from oral, enteral, and parenteral sources other than Numeta); 3) adverse

⁵⁹ 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

⁶⁰ In accordance with Article 107p-q of Directive 2001/83/EC

⁶¹ Alanine, arginine, aspartic acid, cysteine, glucose anhydrous, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, olive oil refined, ornithine, phenylalanine, proline, serine, sodium chloride, sodium glycerophosphate hydrated, soya bean oil refined, taurine, threonine, tryptophan, tyrosine, valine, potassium acetate, calcium chloride dihydrate, magnesium acetate tetrahydrate

events (AEs) and serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory results and CS abnormal vital signs] as per the request for supplementary information (RSI) adopted in June 2018

Background

Numeta G16%E emulsion for infusion is a nationally authorised product that was subject to a referral procedure under Article 107i of Directive 2001/83/EC, which concluded in September 2013 (see [EMA/564255/2013](#)). The conclusion of the referral requested (see [Annex V](#)) a prospective non-interventional PASS to further evaluate magnesium (Mg) levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice. A protocol dated 3 July 2014 for study 7032-001 was endorsed by the PRAC on 10 July 2014. For further background, see [PRAC minutes February 2014](#), [PRAC minutes May 2014](#), [PRAC minutes June 2014](#) and [PRAC minutes July 2014](#).

The final study report was submitted to EMA by MAH Baxter with an update of the RMP and the product information (PI) resulting from the data presented in this PASS final study report. The PRAC discussed the final study results. For further background, see [PRAC minutes March 2018](#) and [PRAC minutes June 2018](#).

Summary of advice

- Based on the review of the final report of the PASS entitled 'a multicentre, non-interventional, uncontrolled, open-label, observational study in children (up to age 24 months) to evaluate serum Mg levels associated with the intake of Numeta G16%E' version dated 31 October 2017, together with the MAH's responses to the request for supplementary information, the PRAC considered that the benefit-risk balance of medicinal products containing the active substances alanine/arginine/aspartic acid/calcium chloride dihydrate/cysteine/glucose anhydrous/glutamic acid/glycine/histidine/isoleucine/leucine/lysine/magnesium acetate tetrahydrate/methionine/olive oil refined/ornithine/phenylalanine/potassium acetate/proline/serine/sodium chloride/sodium glycerophosphate hydrated/soya bean oil refined/taurine/threonine/tryptophan/tyrosine/valine concerned by the PASS final report remains unchanged.
- Nevertheless, the PRAC recommended that the terms of the marketing authorisation(s) should be varied to remove the condition set in Annex IV to conduct the above mentioned study. In addition, the MAH should submit an updated RMP at the next regulatory opportunity in order to address that this condition has been fulfilled. As a result of the fulfilment of the study, the product should be removed from the list of medicines under additional monitoring.

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁶²

See also Annex I 17.4.

7.4.1. Zoledronic acid - ACLASTA (CAP) - EMEA/H/C/000595/II/0069

Applicant: Novartis Europharm Limited

⁶² In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final 5-year report for study ZOL446H2422 (listed as a category 3 study in the RMP): a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta (zoledronic acid) against oral bisphosphonates and untreated population controls

Background

Aclasta is a centrally authorised medicine containing zoledronic acid, a bisphosphonate. Aclasta (zoledronic acid) is indicated for the treatment of osteoporosis in post-menopausal women and adult men at increased risk of fracture, including those with a recent low-trauma hip fracture, for the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women, in adult men, at increased risk of fracture as well as for the treatment of Paget's disease of the bone in adults.

As stated in the RMP of Aclasta (zoledronic acid), the MAH conducted a non-interventional PASS using health registries to compare the safety of Aclasta (zoledronic acid) with oral bisphosphonates and untreated population controls. The Rapporteur assessed the MAH's final study report.

Summary of advice

- The PRAC discussed the assessment of the MAH's response to the second request for supplementary information (RSI) and of the final 5-year study report of the category 3 observational cohort study based on national registries in Denmark and Sweden to evaluate the relative risks of diagnoses pertaining to cardiovascular, cerebrovascular safety and skeletal safety in patients prescribed Aclasta (zoledronic acid) versus oral bisphosphonates and untreated population controls.
- The Committee fully endorsed the assessment and conclusions made by the PRAC Rapporteur. The study addressed the request for follow-up of cardiovascular, cerebrovascular and fracture events and based on the assessment of the final study results no labelling change, in relation to fractures, osteonecrosis of the jaw, heart failure and all-cause mortality is required. The limitations of this study in terms of residual confounders which could not be addressed despite in depth analyses were fully acknowledged by the Committee.

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

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

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

7.8. Ongoing Scientific Advice

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

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

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

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

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See Annex I 18.3.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

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

9.3. Others

None

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

10.1. Safety related variations of the marketing authorisation

10.1.1. Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0073

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Julie Williams

Scope: PRAC follow-up consultation on a variation to update sections 4.6 and 5.3 of the SmPC as requested in the conclusions of the PSUSA procedure (PSUSA/00010373/201703) adopted by PRAC at its November 2017 meeting in order to include revised safety information about pregnancy and risk of malformative or foetal toxicity. The package leaflet is updated accordingly

Background

Isentress is a centrally authorised medicine containing raltegravir, a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 InSTI). Isentress (raltegravir), in combination with other anti-retroviral medicinal products, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection under certain conditions.

Following the review of the latest PSUR for raltegravir-containing products (procedure PSUSA/00010373/201703, see [PRAC minutes November 2017 \(23-26 October 2017\)](#), the MAH was requested to submit to EMA additional data and/or additional analysis to demonstrate the safe use of raltegravir in pregnancy and the lack of potential for foetotoxicity and to update the product information accordingly via a type II variation. This variation proposing to update the product information is under evaluation at the CHMP (EMA/H/C/000860/II/0073) and the PRAC was requested to provide advice to CHMP. For further background, see [PRAC minutes July 2018](#). At its July 2018 meeting, the PRAC supported the more precautionous approach that had been advocated by the PRAC Rapporteur, which reflected the data submitted by the MAH but also was taken in light of the recent concerns that had arisen regarding the signal of increased risk of neural tube defects with dolutegravir when taken prior to conception. The update provided by the MAH included further data for consideration and an alternative proposal for summary of product characteristics wording. It is considered that the data included in the update provides some reassurance on the safety of the product during pregnancy and that the wording proposed by the company for the product information is in line with the 'CHMP guideline on risk assessment of medicinal products on human reproduction and lactation' and acceptable.

Summary of advice

- The PRAC noted that the MAH had accepted to keep the sentence stating that 'studies in animals have shown reproductive toxicity' in the product information section on pregnancy and lactation.
- Regarding clinical data, based on the data presented no safety concerns emerged from the review of those reports. However, taking into account the recent signal of neural tube defects associated with dolutegravir following exposure prior to or at the time of conception, the PRAC stressed the importance of closely monitoring this risk with all integrase inhibitors, including raltegravir.
- The PRAC noted that the available data related only to experience with use of doses of 400mg given twice daily and it was noted that there were no data available for the 600mg tablets, the 25mg and 100mg chewable tablets and the granules for oral suspension. The PRAC considered that based on the available data which did not suggest an increased risk of birth defects, spontaneous abortion or stillbirth, the product information section on pregnancy and lactation for formulations where the daily dose would not exceed 800mg (granules for oral suspension, 25mg and 100mg chewable tablets and 400mg tablets) should state 'raltegravir 400mg twice daily should be used

during pregnancy only if the expected benefit justifies the potential risk to the foetus'. With regards to the 25mg and 100mg chewable tablets and the granules for oral suspension, PRAC advised that the product information should highlight the lack of data for these specific formulations but also make reference to the available data that exist for the 400mg formulation and which are the basis for the recommendations relating to use during pregnancy. Given that there are no data to inform the risk safety of use during pregnancy at doses greater than 800mg per day, it was also advised that for the 600mg tablets (administered twice daily) the product information should reflect this lack of data and that currently use of this formulation during pregnancy should remain as not recommended.

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

None

10.3. Other requests

None

10.4. Scientific Advice

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

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

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Dienogest, ethinylestradiol⁶³ (NAP) - DE/H/xxxx/WS/534

Applicant(s): Bayer Vital GmbH (Celimona, Celimone, Maxim, Valette)

PRAC Lead: Martin Huber

Scope: PRAC follow-up consultation on a worksharing procedure to assess the risk of venous thromboembolism associated with dienogest/ethinylestradiol-containing combined hormonal contraceptives (CHCs) compared to levonorgestrel/ethinylestradiol-containing CHCs

Background

In 2013, the EMA reviewed the risk of venous thromboembolism (VTE) with different progestogen-containing combined hormonal contraceptives (CHCs) within a referral

⁶³ Combined hormonal contraceptive (CHC)

procedure under Article 31 of Directive 2001/83/EC ([EMA/H/A-31/1356](#)), and information about this risk was included in the product information of the medicines. At the time of this review there was not sufficient information about the risk of VTE with products containing dienogest to quantify the risk. However, information has been included in the product information for dienogest/ethinylestradiol (DNG/EE)-containing CHCs that 'limited epidemiological data suggest that the risk of VTE with dienogest-containing CHCs may be similar to the risk with levonorgestrel-containing CHCs', which have the lowest VTE-risk among the CHCs.

Following the recent submission by the MAH Bayer Vital GmbH of results of a meta-analysis of four prospective cohort studies⁶⁴ with similar study design on the risk of VTE associated with the use of CHCs containing DNG/EE and levonorgestrel/ethinylestradiol, performed following the completed referral procedure under Article 31 of Directive 2001/83/EC ([EMA/H/A-31/1356](#)), new information on the known risk of VTE with CHC-containing DNG/EE was identified by Germany. For further background, see [PRAC minutes April 2018](#). In the context of the evaluation of a worksharing type II variation procedure DE/H/xxxx/WS/534 to evaluate the risk of VTE associated with DNG/EE compared to levonorgestrel (LNG)/EE based on the assessment of the results of a meta-analysis of 4 prospective cohort studies with similar study design to investigate the VTE risk in women taking a CHC containing DNG/EE versus the VTE risk in women taking a CHC containing LNG/EE and to further update the product information accordingly, Germany requested PRAC advice on its assessment. For further background, see [PRAC minutes June 2018](#). During its October 2018 meeting, the PRAC discussed the follow-up request for PRAC advice.

Summary of advice

The Committee noted the assessment by the Reference Member State (RMS) as detailed in the provided draft assessment report and supported the proposed way forward:

- The Committee was of the view that it is not necessary to ask the MAH, as part of a second request for supplementary information (RSI), for further discussion on the relevance of polycystic ovary syndrome (PCOS) as a potential confounder in the analysis as this further analysis would not be expected to significantly change the VTE risk estimates associated with DNG/EE and result in different conclusions.
- The warning in the product information (PI) on the risk of VTE should be refined to incorporate further amendments.
- The proposed direct healthcare professional communication (DHPC) and communication plan to inform on the latest evidence of the VTE risk associated with CHC containing DNG/EE, i.e. slightly higher risk of VTE in women using CHC containing DNG/EE compared to users of CHC containing LNG/EE, is supported with further amendments. The PRAC also highlighted that implementation and dissemination of the DHPC should be at the discretion of the concerned Member States. The updates of the existing core elements for communication and education materials for patients implemented by Member States following the CHC referral procedure, i.e. patient sheet Q&A, to include the latest evidence on the VTE risk associated with CHC containing DNG/EE are endorsed.

⁶⁴ LASS study: 'Long-term active surveillance study for oral contraceptives'; INAS-OC study: 'International active surveillance study of women taking oral contraceptives'; TASC study: 'Transatlantic active surveillance on cardiovascular safety of Nuvaring (etonogestrel/ethinylestradiol vaginal ring)'; INAS-SCORE study: 'International active surveillance study – safety of contraceptives: role of estrogens'

- Finally, the Committee supported that further discussion of potentially differential VTE risks between different EE doses across the whole CHC class does not pertain to this ongoing work-sharing variation and that, if necessary, further consideration on this issue may be given at the national level, based on the further evaluation of the data.

11.2.2. Finasteride (NAP) - SE/H/xxxx/WS/243

Applicant(s): Merck Sharp & Dohme BV (Chibro-Proscar, Pilus, Propecia, Proscar, Prostide), various

PRAC Lead: Ulla Wändel Liminga

Scope: PRAC consultation on a worksharing procedure assessing the results of a Nordic register-based nested case-control study examining male breast cancer incidence in finasteride users compared to non-users

Background

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of type II 5 alpha-reductase, an intracellular enzyme that metabolizes the androgen testosterone to dihydrotestosterone (DHT). It is indicated for the treatment and control of benign prostatic hyperplasia (BPH), for the prevention of urologic events under certain conditions, and for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

The Finasteride Nordic Registry study was initiated in 2011 to determine whether an association existed between finasteride exposure and the development of male breast cancer as a PASS following the evaluation of a weak signal of increased breast cancer at the Pharmacovigilance Working Party (PhVWP) in 2009. Following the review of the submitted data various questions remained regarding the methodology and the results precluding a final conclusion regarding the signal that the MAH was asked to address. In the context of the evaluation of the final results and the MAH's answers to the request for supplementary information, assessed in the context of a worksharing type II variation procedure (SE/H/xxxx/WS/243), Sweden requested PRAC advice on its assessment.

Summary of advice

- The PRAC discussed the data submitted by the MAH and assessed within the ongoing worksharing variation, specifically the design and analyses of the study. Although some questions were raised in regards to the exposure time, the PRAC considered that, overall, the MAH had properly accounted for the residual confounding and agreed with the conclusion proposed by Sweden and supported by the study results that there is no causal relationship between finasteride treatment and the risk of male breast cancer.
- Even though the data seems reassuring in terms of causality, the PRAC considered that a precautionary approach in terms of the information available in the product information (PI) would be advisable, and agreed to maintain the current warning⁶⁵ noting that cases of male breast cancer had been reported for finasteride, and requesting physicians to instruct patients to report changes in breast tissue. For consistency, it was suggested to also maintain the similar wording among the

⁶⁵ SmPC section 4.4

undesirable effects description⁶⁶ regarding male breast cancer.

11.2.3. Minocycline (NAP) - ES/H/PSUFU/00002065/201708

Applicant(s): Almirall, Biogaran, Meda, Mylan, Teofarma, Tillomed, various

PRAC Lead: Maria del Pilar Rayon

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on foetal exposure and utilisation of minocycline during pregnancy as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on minocycline (PSUSA/00002065/201708) concluded in May 2018

Background

Minocycline is a tetracycline indicated for the prevention of asymptomatic meningococcal carriers, and of pre- and post-operative infections. In addition, minocycline is indicated for the treatment of acne (including tetracycline resistant acne), skin and soft tissue infections, ophthalmological infections, acute and chronic bronchitis, bronchiectasis, lung abscess, ear, nose and throat infections, pelvic inflammatory disease, nocardiosis, urinary tract infections, gonorrhoea, non-gonococcal urethritis and prostatitis.

At its meeting in May 2018, the PRAC considered that foetal exposure and utilisation during pregnancy needed to be further assessed. For further background, see [PRAC minutes May 2018](#). In the context of the evaluation of the MAHs answers in an informal work-sharing procedure (ES/H/PSUFU/0002065/201708), Spain, as reference Member State (RMS), requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the RMS position that no new warnings are warranted in the product information.

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

⁶⁶ SmPC section 4.8

12.4. Cooperation within the EU regulatory network

12.4.1. Brexit: preparedness of the regulatory network and capacity increase

As a follow-up to previous discussions (see [PRAC minutes November 2017](#), [PRAC minutes January 2018](#), [PRAC minutes May 2018](#) and [PRAC minutes September 2018](#)), the EMA Secretariat provided the PRAC with a status update on the Brexit preparedness business continuity plan, including Committees' operational preparedness activities in view of the withdrawal of the UK from the European Union.

12.4.2. Regulatory science engagement plan to 2025

In line with the [PRAC work plan 2018](#), the EMA Secretariat presented to PRAC the 'EMA regulatory science to 2025' project plan. This focusses on the impact of utilisation of emerging science, technologies/regulatory science tools within product development on the European regulatory landscape over the next 5-10 years together with steps to prepare for this impact. So far, a baseline report has been prepared to identify science and technology trends and regulatory tools in consultation with Committee Chairs. In addition, stakeholders have been interviewed to verify the baseline report's findings and identify any missed trends. This led to a first draft document of the EMA regulatory science to 2025. As part of the next steps, a '[human stakeholder workshop](#)' is organised on 24 October 2018 and by the end of 2018, a 6-month public consultation will be launched. Further updates will be given in due course.

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

12.8.1. Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q3 2018

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see [PRAC minutes January 2018](#).

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 GPAG, focussing on harmonising and streamlining the EURD list.

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 October 2018, 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 October 2018, the updated EURD list was adopted by the CHMP and CMDh at their October 2018 meetings and published on the EMA website on 23 October 2018, see:

[Home> Human Regulatory>Post-authorisation>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

The PRAC was updated on the signal management review technical (SMART) working group meeting held on 1 October 2018. The discussion focussed mainly on the handling of signals with no plenary discussion, on confirmation step for signals dealt with other procedures as

well as on draft recommendations referring to a need for a direct healthcare professional communication (DHPC). It was stressed that any outcome assessment report and recommendations should ensure that DHPC, communication plan, agreed 'key elements' or any other communication tool means (e.g. bulletins) are clearly stated as applicable.

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

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 31 October 2018 on the EMA website (see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management plan (RMP) template for industry - revision

At the organisational matters teleconference held on 18 October 2018, and in line with the [PRAC work plan 2018](#), the EMA Secretariat presented to the Committee revision 2.01 of the guidance on the format of RMP in the EU (template), previously adopted as revision 2 in 2017 (see [PRAC minutes March 2017](#)). The adoption of the document is planned at the November 2018 PRAC meeting (to be held on 29-31 October).

12.14.2. Risk management systems

None

12.14.3. Risk minimisation measures: Patient alert cards and patient reminder cards - clarification

In the context of the Agency's measures and business continuity plan (BCP) as part of the Brexit preparedness (for further background, see [PRAC minutes September 2018](#)) and the temporary suspension of the current development of revision 3 of GVP module XVI on 'risk

minimisation measures: selection of tools and effectiveness indicators' (see [PRAC work plan 2018](#)), the EMA Secretariat presented at the organisational matters teleconference held on 18 October 2018 clarifications on the use of patient alert cards (PAC) and patient reminder cards (PRC). The PRAC discussed the matter and made some suggestions that will be taken on board when the revision of GVP module XVI is reinstated after the end of EMA BCP. Further discussion will follow in due course.

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

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. Public participation in pharmacovigilance

None

12.18.2. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific considerations III: risk management in pregnant and breastfeeding women - Update

At the organisational matters teleconference held on 18 October 2018, and in line with the [PRAC work plan 2018](#), the EMA Secretariat presented to PRAC a status update of the draft 'GVP product- or population- specific considerations III: risk management in pregnant and breastfeeding women' document together with a proposed timetable towards the launch of a public consultation. A follow-up discussion is planned in November/December 2018.

13. Any other business

Next meeting on: 29-31 October 2018

14. Annex I – Signals assessment and prioritisation⁶⁷

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 timetables⁶⁸.

14.1.1. Avelumab – BAVENCIO (CAP)

Applicant(s): Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of pancreatitis

EPITT 19291 – New signal

Lead Member State(s): DK

14.1.2. Tocilizumab – ROACTEMRA (CAP)

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of facial paralysis

EPITT 19295 – New signal

Lead Member State(s): DE

⁶⁷ 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

⁶⁸ 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

14.2. New signals detected from other sources

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. Tobramycin - EMEA/H/C/005086

Scope: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis (CF)

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. Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0030

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Update of the RMP (version 4.3) as requested by CHMP in variation II/25/G (REC 014) concluded in February 2018. In addition, the MAH took the opportunity to extend the due date of the final clinical study report for the specific obligation (SOB) for the single arm open-label multicentre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. Annex II is updated accordingly

15.2.2. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/WS1441/0034; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide - GENVOYA (CAP) - EMEA/H/C/004042/WS1441/0051; emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/WS1441/0035; tenofovir alafenamide - VEMLIDY (CAP) - EMEA/H/C/004169/WS1441/0016

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 3.1 for Vemlidy, Descovy and Odefsey, as well as version 3.3 for Genvoya) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template) in order

to revise the safety concerns in alignment with the approved RMP for Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide). In addition, the MAH took the opportunity to update the deliverable milestones for study GS-US-311-1269 (listed as a category 3 study in the RMP): a phase 2/3, open-label, multi-cohort switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in human immunodeficiency virus 1 (HIV-1) infected children and adolescents virologically suppressed on a 2-nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen as well as to amend the address of the MAH

15.2.3. Evolocumab - REPATHA (CAP) - EMEA/H/C/003766/II/0028

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Update of the RMP (version 5.0) in order to provide the final results of study 20120332 (GAUSS-3, part C) (listed as a category 3 study in the RMP): a 3-part, phase 3, multicentre, randomized, double-blind, ezetimibe-controlled, parallel-group study. Part C was a 2-year, open-label extension that evaluated the long-term safety and efficacy of evolocumab in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. As a consequence, the MAH proposes to remove missing information of use in patients with severe hepatic impairment (Child-Pugh class C) and use in patients with hepatitis C

15.2.4. Human fibrinogen, human thrombin - EVICEL (CAP) - EMEA/H/C/000898/II/0063

Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 14.2) in order bring it in line with revision 2 of the guidance on the format of RMP in the EU (template) to update exposure data, and reflect the PRAC outcome for procedure PSUSA/00010297/201706 adopted in January 2018 (removal of lack of efficacy as identified risk, reclassification and/or removal of risk from the safety specification)

15.2.5. Pregabalin - LYRICA (CAP) - EMEA/H/C/000546/WS1364/0092; PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/WS1364/0021

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Update of the RMP (version 12.0) in order to include the changes requested in the conclusions of EMEA/H/C/PSUSA/00002511/201701 procedure finalised in September 2017, updating the safety specifications and risk minimisation measures. The pharmacovigilance plan is also updated. The draft protocol for a non-interventional non-imposed PASS (A0081359) entitled 'a population-based cohort study of pregabalin to characterize pregnancy outcomes' is submitted. The MAH took the opportunity to include minor updates and to align the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

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).

15.3.1. Alirocumab - PRALUENT (CAP) - EMEA/H/C/003882/II/0042

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease based on the final study report of study EFC11570: a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet and RMP (version 4.0) are updated accordingly

15.3.2. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0106/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC to reflect final overall survival data from the long-term follow-up study JO25567 (erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations: an open-label, randomised, multicentre, phase 2 study) in order to fulfil ANX 085 for study JO29424 (survival follow up of JO25567); 2) change in the deadline for the fulfilment of ANX 086 (discussion on any further outcome data on the combination of bevacizumab and erlotinib in the first-line treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations) from Q4 2018 to Q2 2019. Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 29.0) are updated accordingly. The RMP is submitted in line with revision 2 of the guidance on the format of RMP in the EU (template) and consolidates the approved versions (versions 27.1 and 28.1)

15.3.3. Cetuximab - ERBITUX (CAP) - EMEA/H/C/000558/II/0082

Applicant: Merck KGaA

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.4 and 4.8. of the SmPC regarding the existing warning on interstitial lung disease (ILD) by specifying potentially fatal ILD outcome, patients with contributory factors at risk of fatal events and need for close monitoring of these patients. The RMP (version 19.0) is updated accordingly including further changes as per the conclusions of the latest PSUSA procedure (PSUSA/00000635/201739) finalised in May 2018. The MAH also took the opportunity to update Annex II-D on 'conditions or restrictions with

regard to the safe and effective use of the medicinal product' to delete an obsolete sentence referring to a RMP to be submitted in 2014

15.3.4. Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from the paediatric study DACOGENAML2004: a phase 1-2 safety and efficacy study of Dacogen (decitabine) in sequential administration with cytarabine in children with relapsed or refractory acute myeloid leukaemia' as per the requirement of Article 46 of Regulation (EC) No1901/2006. The RMP (version 3.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template). In addition, the MAH took the opportunity to update section 4.4 of the SmPC to align the safety warning related to sodium excipient with the Annex to the revised European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly. Moreover, the contact details of the local representative in Slovenia are updated in the package leaflet

15.3.5. Efmoroctocog alfa - ELOCTA (CAP) - EMEA/H/C/003964/II/0026

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to add a statement for a once-weekly prophylaxis dose and to update the safety information based on the final results from study 8HA01EXT (listed as a category 3 study in the RMP): an interventional study that evaluated the long-term safety (particularly immunogenicity) and efficacy of Elocta (efmoroctocog alfa) in the prevention and treatment of bleeding episodes and for perioperative management. The RMP (version 2.1) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.6. Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0002

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII (FVIII) inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the following pivotal trials: 1) study BH30071 (HAVEN 3): an ongoing, multicentre, open-label, randomized phase 3 clinical study evaluating the efficacy, safety and pharmacokinetic (PK) of emicizumab prophylaxis at doses of 1.5 mg/kg/week (QW) and 3 mg/kg/every 2 weeks (Q2W) versus no prophylaxis in adults and adolescent patients (age of 12 or above) with haemophilia A without inhibitors against FVIII; 2) study BO39182 (HAVEN 4): an ongoing multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab given as the dose of 6 mg/kg/every 4 weeks (Q4W) in adults and adolescent patients (age of 12 or above) with haemophilia A with or without FVIII inhibitors; 3) study BH29992 (HAVEN 2): a multicentre, open-label, non-

randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab at the QW dose in paediatric patients (<12 years old or 12-17 years old and <40kg) with haemophilia A with FVIII inhibitors. The package leaflet and the RMP (version.2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC

15.3.7. Eptacog alfa (activated) - NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0104

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to extend patient population of NovoSeven (eptacog alfa) for use in patients with Glanzmann's thrombasthenia without antibodies to platelets, or where platelets are not readily available, based on a prospective observational registry and literature references. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in section 4.8 of the SmPC and in package leaflet

15.3.8. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0073/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.5 and 4.8 of the SmPC in order to include new safety information on cardiac arrhythmias based on safety signal assessment report (SSAR); 2) update of section 4.8 of the SmPC to update the frequency of some adverse events (AEs) based on data obtained from the updated safety pool analysis (Pool DBC-1) which consists of the combined data from SP667, SP754, SP755, and EP0008. All of these studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive therapy studies in subjects with epilepsy. The package leaflet and the RMP (version 13.0) are updated accordingly

15.3.9. Methoxy polyethylene glycol-epoetin beta - MIRCERA (CAP) - EMEA/H/C/000739/II/0068

Applicant: Roche Registration GmbH

PRAC Rapporteur: Eva Segovia

Scope: Submission of the final report for study BH21260 (listed as a category 3 study in the RMP): a randomized, controlled, open-label, multicentre, parallel-group study to assess all-cause mortality and cardiovascular morbidity in patients with chronic kidney disease (CKD) on dialysis and those not on renal replacement therapy under treatment with Mircera (methoxy polyethylene glycol-epoetin beta) or erythropoiesis-stimulating agents (ESAs) of reference (in fulfilment of post-approval commitment MEA 008.5). The RMP (version 12.0) is updated accordingly and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.10. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0035

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4., 4.8 and 5.1 of the SmPC in order to update the safety information and to add urticaria as an adverse reaction following the final results from study POX-MVA-037 (listed as a category 3 study in the RMP (post-authorisation measure MEA 007)): a phase 2, randomized, open-label, multicentre trial designed to evaluate the safety and immunogenicity of Imvanex (modified vaccinia Ankara-Bavarian Nordic (MVA-BN) live virus smallpox vaccine) when increasing the dose or the number of injections compared with the standard 2-dose regimen in a population of adult, vaccinia naïve, immunocompromised subjects with human immunodeficiency virus (HIV) infection. The RMP (version 7.1) is updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10)

15.3.11. Modified vaccinia Ankara virus - IMVANEX (CAP) - EMEA/H/C/002596/II/0036

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and to provide confirmation in terms of immunogenicity based on the results from study POX-MVA-006 (listed as an obligation in Annex II (ANX 004)): a randomized, open-label phase 3 non-inferiority trial to compare indicators of efficacy for smallpox vaccine to the US licensed replicating smallpox vaccine in 18-42 year old healthy vaccinia-naïve subjects. The package leaflet and the RMP (version 7.2) are updated accordingly

15.3.12. Pegaspargase - ONCASPAR (CAP) - EMEA/H/C/003789/II/0016/G

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Grouped variations consisting of an update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC with the final results from 2 studies, namely: 1) study DFCI 11-001 (listed as a category 3 study in the RMP): a phase 2, open-label, randomized, multicentre study to determine the safety and feasibility of administering an investigational asparaginase product (asparaginase formulation) compared with Oncaspar (pegaspargase) in subjects aged 1 to <22 years with newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma; 2) study AALL07P4 (listed as a category 3 study in the RMP): a multicentre, open label, randomized, active-controlled, parallel design clinical pilot study conducted to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy of an investigational asparaginase product in comparison with Oncaspar (pegaspargase) in patients aged 1 to <31 years newly diagnosed with high risk B-precursor ALL. The package leaflet and the RMP (version 3.0) are updated accordingly

15.3.13. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/II/0046

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning and

safety information on 'anaphylaxis'. The RMP is updated accordingly (version 3.2)

15.3.14. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0057

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) tumours expressing programmed death-ligand 1 (PD-L1) with a $\geq 1\%$ tumour proportion score (TPS) based on data from study KEYNOTE-042: an international, randomized, open-label phase 3 study investigating Keytruda (pembrolizumab) monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS $\geq 1\%$) NSCLC, and on supportive data from the final planned analysis of KEYNOTE-024: a phase 3 randomized open-label study of Keytruda (pembrolizumab) monotherapy compared to platinum-based chemotherapy in metastatic NSCLC with PD-L1 TPS $\geq 50\%$. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The RMP is updated accordingly (version 18.1)

15.3.15. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0058

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.4 of the SmPC to include in the existing warning regarding immune-related adverse reactions the fact that these reactions may be fatal in patients treated with pembrolizumab. The package leaflet is updated accordingly, and for consistency with the already existing statement in SmPC section 4.4, the package leaflet also includes that immune-related adverse reactions can occur after discontinuation of pembrolizumab treatment. The RMP is updated accordingly (version 19.1)

15.3.16. Pomalidomide - IMNOVID (CAP) - EMEA/H/C/002682/II/0031/G, Orphan

Applicant: Celgene Europe Limited

PRAC Rapporteur: Patrick Batty

Scope: Grouped applications consisting of: 1) extension of indication to include treatment with Imnovid (pomalidomide) in combination with bortezomib and dexamethasone of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 15.0) are updated accordingly; 2) addition of 14-capsule pack sizes for the 1 mg, 2 mg, 3 mg and 4 mg strengths to support the proposed posology and pomalidomide dose modification. The SmPC, labelling and package leaflet are updated accordingly; 3) update of section 5.1 of the SmPC in order to update the information on pomalidomide mechanism of action based on literature data

15.3.17. Regadenoson - RAPISCAN (CAP) - EMEA/H/C/001176/II/0027

Applicant: GE Healthcare AS

PRAC Rapporteur: Patrick Batty

Scope: Extension of indication to include use in the measurement of fractional flow reserve (FFR) during invasive coronary angiography (ICA) in patients presenting a coronary artery stenosis based on results from study 060912001: a comparison of Rapiscan (regadenoson) and central intravenous adenosine for measurement of fractional flow reserve and data from published literature. 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 10.0) are updated accordingly

15.3.18. Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/X/0006/G

Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to add new strengths of 2500 IU, 3000 IU and 4000 IU, powder and solvent for solution for injection; 2) update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect available data from previously untreated patients (PUP) from GENA-05 (immunogenicity, efficacy and safety of treatment with human cell line-derived recombinant factor VIII (human-cl rhFVIII) in previously untreated patients with severe haemophilia A) (interim report) study; 3) update of the RMP (version 10) to align the content in a single harmonised worldwide version for simocotocg alfa (recombinant factor VIII (rFVIII)); 4) update of the product information as per the outcome of the referral procedure under Article 31 of Directive 2001/83/EC finalised in 2017 (EMEA/H/A-31/1448)

15.3.19. Tedizolid phosphate - SIVEXTRO (CAP) - EMEA/H/C/002846/II/0027

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.8 of the SmPC in order to add safety information based on the final results from study 16099 (listed as a post-authorisation efficacy study (PAES) in the RMP): a prospective, randomized, open-label, active-controlled, multicentre study to evaluate the efficacy and safety of tedizolid in Japanese patients with methicillin-resistant Staphylococcus aureus (MRSA) infections (skin and soft tissue infection (SSTI) and SSTI-related bacteraemia). The RMP (version 4.0) is updated accordingly in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3.20. Thalidomide - THALIDOMIDE CELGENE (CAP) - EMEA/H/C/000823/II/0056, Orphan

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of the RMP (version 19) in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of RMP in the EU (template) to propose the reclassification and/or renaming of known safety concerns associated with the use of thalidomide. Consequently, Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product', section 4.4 and 4.6 of the SMPC as well as the package leaflet are updated accordingly

15.3.21. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/II/0028

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Update of sections 4.1, 4.4 and 5.1 of the SmPC in order to delete the information regarding rearranged during transfection (RET) mutation. The application fulfils SOB 001 and includes a proposal to revert from conditional to marketing authorisation to standard marketing authorisation. Annex II, the package leaflet and the RMP (version 12.2) are updated accordingly. In addition, the MAH took the opportunity to bring the product information in line with the latest QRD template (version 10)

15.3.22. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/II/0034

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of section 5.1 of the SmPC in order to provide the final efficacy results up to week 348 regarding clinical study c13008 (listed as a category 3 study in the RMP): a phase 3, open-label study to determine the long-term safety and efficacy of vedolizumab in subjects with ulcerative colitis and Crohn's disease. The RMP is updated accordingly (version 4.0)

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. 5-aminolevulinic acid⁶⁹ - GLIOLAN (CAP) - PSUSA/00000009/201803

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

⁶⁹ Indicated in the treatment of glioma

16.1.2. Albiglutide - EPERZAN (CAP) - PSUSA/00010175/201803

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.3. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201803

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.4. Belimumab - BENLYSTA (CAP) - PSUSA/00009075/201803

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.5. Bosutinib - BOSULIF (CAP) - PSUSA/00010073/201803

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.6. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/201803

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.1.7. Cangrelor - KENGREXAL (CAP) - PSUSA/00010360/201803

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.8. Ceftolozane, tazobactam - ZERBAXA (CAP) - PSUSA/00010411/201803

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.9. Cholic acid⁷⁰ - KOLBAM (CAP) - PSUSA/00010182/201803

Applicant: Retrophin Europe Ltd
PRAC Rapporteur: Patrick Batty
Scope: Evaluation of a PSUSA procedure

16.1.10. Ciclosporin⁷¹ - IKERVIS (CAP) - PSUSA/00010362/201803

Applicant: Santen Oy
PRAC Rapporteur: Julie Williams
Scope: Evaluation of a PSUSA procedure

16.1.11. Dabigatran - PRADAXA (CAP) - PSUSA/00000918/201803

Applicant: Boehringer Ingelheim International GmbH
PRAC Rapporteur: Anette Kirstine Stark
Scope: Evaluation of a PSUSA procedure

16.1.12. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201803

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

16.1.13. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201803

Applicant: Sanofi-aventis groupe
PRAC Rapporteur: Kimmo Jaakkola
Scope: Evaluation of a PSUSA procedure

16.1.14. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201803

Applicant: Swedish Orphan Biovitrum AB (publ)
PRAC Rapporteur: Brigitte Keller-Stanislawski
Scope: Evaluation of a PSUSA procedure

16.1.15. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201803

Applicant: Allergan Pharmaceuticals International Ltd

⁷⁰ Indicated in the treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacetyl-CoA racemase (AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency

⁷¹ Topical use only

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.16. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201803

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.17. Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - PSUSA/00010653/201803

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.18. Glycopyrronium⁷² - SIALANAR (CAP) - PSUSA/00010529/201803

Applicant: Proveca Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.19. Guanfacine - INTUNIV (CAP) - PSUSA/00010413/201803

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.20. Guselkumab - TREMFYA (CAP) - PSUSA/00010652/201803

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.21. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201803

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

⁷² Centrally authorised product(s) only, indicated for the treatment of severe sialorrhoea

16.1.22. Influenza vaccine⁷³ (split virion, inactivated) - INTANZA⁷⁴ (CAP) - PSUSA/00001743/201803

Applicant: Sanofi Pasteur Europe

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

16.1.23. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/201803

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.24. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201803

Applicant: Basilea Medical Limited

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.25. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201803

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.26. Lapatinib - TYVERB (CAP) - PSUSA/00001829/201803

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.27. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201803

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.28. Midostaurin - RYDAPT (CAP) - PSUSA/00010638/201803

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

⁷³ Centrally authorised product(s) only

⁷⁴ European Commission (EC) decision on the MA withdrawal of Intanza dated 3 August 2018

Scope: Evaluation of a PSUSA procedure

16.1.29. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201803

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

16.1.30. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201803

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.1.31. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201803

Applicant: Rempex London Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.32. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁷⁵) - EMEA/H/W/002300/PSUV/0033

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUR procedure

16.1.33. Tobramycin⁷⁶ - VANTOBRA (CAP) - PSUSA/00010370/201803

Applicant: Pari Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.34. Tolcapone - TASMAR (CAP) - PSUSA/00002985/201803

Applicant: Meda AB

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

⁷⁵ 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)

⁷⁶ Centrally authorised product(s) only, nebuliser solution only

16.1.35. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/201803

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.36. Vildagliptin - GALVUS (CAP); JALRA (CAP); XILIRX (CAP); vildagliptin, metformin - EUCREAS (CAP); ICANDRA (CAP) ; ZOMARIST (CAP) - PSUSA/00003113/201802

Applicant: Novartis Europharm Limited

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. Atosiban - TRACTOCILE (CAP); NAP - PSUSA/00000264/201801

Applicants: Ferring Pharmaceuticals A/S (Tractocile), various

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.2.2. Dexrazoxane - SAVENE (CAP); NAP - PSUSA/00001001/201802

Applicants: Clinigen Healthcare Ltd (Savene), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.3. Trientine - CUPRIOR (CAP); NAP - PSUSA/00010637/201803

Applicants: GMP-Orphan SA (Cuprior), various

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

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

16.3.1. Amitriptyline hydrochloride, chlordiazepoxide (NAP) - PSUSA/00000171/201802

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.2. Argatroban (NAP) - PSUSA/00009057/201801

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.3. Cilostazol (NAP) - PSUSA/00010209/201802

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.4. Ciprofloxacin⁷⁷ (NAP) - PSUSA/00000776/201801

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.3.5. Dacarbazine (NAP) - PSUSA/00000919/201802

Applicant(s): various

PRAC Lead: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.3.6. Ethinylestradiol, gestodene⁷⁸ (NAP) - PSUSA/00010145/201802

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.7. Fenoterol, ipratropium (NAP) - PSUSA/00001367/201802

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.8. Human coagulation factor VIII⁷⁹ (NAP) - PSUSA/00009174/201802

Applicant(s): various

PRAC Lead: Daniela Philadelphy

⁷⁷ Topical use only

⁷⁸ Transdermal application only

⁷⁹ Inhibitor bypassing fraction

Scope: Evaluation of a PSUSA procedure

16.3.9. Hydrochlorothiazide, losartan (NAP) - PSUSA/00001655/201802

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.10. Hydroxyethyl starch (NAP) - PSUSA/00001694/201803

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

16.3.11. Iloprost⁸⁰ (NAP) - PSUSA/00009190/201801

Applicant(s): various

PRAC Lead: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.3.12. Lisdexamfetamine (NAP) - PSUSA/00010289/201802

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

16.3.13. Lomustine (NAP) - PSUSA/00001902/201801

Applicant(s): various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

16.3.14. Mivacurium (NAP) - PSUSA/00002077/201801

Applicant(s): various

PRAC Lead: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

16.3.15. Nafarelin (NAP) - PSUSA/00002105/201802

Applicant(s): various

PRAC Lead: Karen Pernille Harg

⁸⁰ Intravenous (I.V) solution only

Scope: Evaluation of a PSUSA procedure

16.3.16. Olodaterol (NAP) - PSUSA/00010245/201803

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.3.17. Tauroselcholic [⁷⁵Se] acid (NAP) - PSUSA/00010486/201801

Applicant(s): various

PRAC Lead: Julia Pallos

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)⁸¹

17.1.1. Chlormadinone acetate, ethinylestradiol (NAP) - EMEA/H/N/PSA/J/0030.1

Applicant: Gedeon Richter Plc (multiple product names)

PRAC Rapporteur: Martin Huber

Scope: MAH's response to S/0060 [amendment to a protocol previously agreed by PRAC in January 2016 for a case control study comparing levonorgestrel and chlormadinone acetate in order to evaluate the role of oral contraceptives and the Risk of Venous Thromboembolism (VTE) (RIVET CC study), to include additional countries, update the study milestones and the statistical analysis plan (SAP) as per the advice by PRAC adopted in January 2018 on the assessment of the first PASS progress report] as per the request for supplementary information (RSI) adopted in June 2018

17.1.2. Tolvaptan – JINARC (CAP) - EMEA/H/C/PSA/S/0031

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Amendment to a protocol initially endorsed by PRAC in March 2016

⁸¹ In accordance with Article 107n of Directive 2001/83/EC

(EMA/H/C/PSP/0028.2) for a 4-year, multicentre, non-interventional PASS to measure the effectiveness of the risk minimisation measures in reducing the severity of liver injury in patients who experience an elevation of transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) > 3× upper limit of normal (ULN), or an adverse event (AE) consistent with hepatotoxicity in real life

17.1.3. Velmanase alfa – LAMZEDE (CAP) - EMA/H/C/PSP/S/0060.1

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: MAH's response to S/0060 [protocol for the alfa-mannosidosis registry: a multicentre, multi-country, non-interventional, prospective cohort, in alfa-mannosidosis patients to evaluate the long-term effectiveness and safety profile of treatment with Lamzedo (velmanase alfa) under conditions of routine clinical care and to characterize the entire alfa-mannosidosis population, including variability of clinical manifestation, progression and natural history] as per the request for supplementary information (RSI) adopted in June 2018

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁸²

17.2.1. Agalsidase beta - FABRAZYME (CAP) - EMA/H/C/000370/MEA 060.4

Applicant: Genzyme Europe BV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 060.3 [protocol for a survey to assess the effectiveness of the patient home infusion educational materials in EU countries where the material is implemented [report submission due date: March 2019]] as per the request for supplementary information (RSI) adopted in May 2018

17.2.2. Baricitinib - OLUMIANT (CAP) - EMA/H/C/004085/MEA 003.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 003.1 [protocol for an observational safety study using an existing database, study I4V-MC-B004: a retrospective cohort study to assess the long-term safety of baricitinib compared with other therapies used in the treatment of adults with moderate-to-severe rheumatoid arthritis in the course of routine clinical care [final report due date: 31/03/2031]] as per the request for supplementary information (RSI) adopted in May 2018

17.2.3. Baricitinib - OLUMIANT (CAP) - EMA/H/C/004085/MEA 004.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

⁸² 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

Scope: MAH's response to MEA 004.1 [protocol for assessing the effectiveness of the patient alert card and healthcare professional educational material, study I4V-MC-B010: a rheumatologist survey to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib); and objective 3 of study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries [final report anticipated within 4 months following the end of data]] as per the request for supplementary information (RSI) adopted in May 2018

17.2.4. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 005.2

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 005.1 [protocol for an observational post marketing disease registry in EU patients, study I4V-MC-B011: a retrospective cohort study to assess the safety of baricitinib compared with other therapies used in the treatment of rheumatoid arthritis in Nordic countries] as per the request for supplementary information (RSI) adopted in May 2018

17.2.5. Cinacalcet - MIMPARA (CAP) - EMEA/H/C/000570/MEA 035

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20180204: a registry study to evaluate the risk of hypocalcaemia in paediatric patients treated with cinacalcet

17.2.6. Dapagliflozin - EDISTRIDE (CAP) - EMEA/H/C/004161/MEA 012.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of a PASS protocol including the MAH's response to MEA 012 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) 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 type 2 diabetes mellitus (T2DM); 2) 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 T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) 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 cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May

2018

17.2.7. Dapagliflozin - FORXIGA (CAP) - EMEA/H/C/002322/MEA 024.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of a PASS protocol including the MAH's response to MEA 024 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) 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 type 2 diabetes mellitus (T2DM); 2) 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 T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) 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 cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

17.2.8. Dapagliflozin, metformin - EBYMECT (CAP) - EMEA/H/C/004162/MEA 011.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol including the MAH's response to MEA 011 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) 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 type 2 diabetes mellitus (T2DM); 2) 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 T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) 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 cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

17.2.9. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/MEA 014.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Submission of a PASS protocol including the MAH's response to MEA 014 [statistical analysis plan (SAP) for the meta-analysis for incidence of amputation and assessment of potential relevant preceding adverse events of interest for the following studies, namely: 1) 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 type 2 diabetes mellitus (T2DM); 2) 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 T2DM, cardiovascular disease and hypertension who exhibit inadequate glycaemic control on usual care; 3) 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 cardiovascular disease, who exhibit inadequate glycaemic control on usual care, in line with the conclusions of the procedure under Article 20 of Regulation (EC) No 726/2004 on sodium-glucose co-transporter-2 (SGLT2) inhibitors completed in 2017 (A-20/1442/C/4161)] as per the request for supplementary information (RSI) adopted in May 2018

17.2.10. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.6

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

17.2.11. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 011.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.1 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients

with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

17.2.12. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMA/H/C/003833/MEA 003.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 011.1 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

17.2.13. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMA/H/C/003833/MEA 004.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

17.2.14. Empagliflozin, metformin - SYNJARDY (CAP) - EMA/H/C/003770/MEA 003.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Amendment to previously agreed protocol for study 1245.96 protocol (version 5.0):

an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors as requested in the outcome of the assessment of the second annual interim report adopted in September 2017

17.2.15. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 007.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 011.1 [revised statistical analysis plan (SAP) and submission of protocol for a meta-analysis of three clinical trials: 1) study 1245.25: a phase 3, multicentre, international, randomised, parallel group, double-blind cardiovascular safety study of empagliflozin (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (EMPA REG); 2) study 1245.110: a phase 3 randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF) (EMPEROR-Preserved) and 3) study 1245.121: a randomised study on efficacy and safety of empagliflozin compared to placebo in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced), including a graph of the cumulative incidence of amputation events and relevant preceding adverse events of special interest (AESI including gangrene, osteomyelitis) over time, to further characterise the important potential risk of lower limb amputation, as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMEA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in April 2018

17.2.16. Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 002.1

Applicant: Tesaro UK Limited

PRAC Rapporteur: Patrick Batty

Scope: MAH's response to MEA 002 [protocol for study 3000-04-001: a non-interventional PASS to evaluate the risks of myelodysplastic syndrome/acute myeloid leukaemia and secondary primary malignancies in adult patients with relapsed ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula (niraparib)] as per the request for supplementary information (RSI) adopted in May 2018

17.2.17. Sonidegib - ODOMZO (CAP) - EMEA/H/C/002839/MEA 021.2

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Amendment to the previously agreed protocol in July 2016 for study CLDE225A2404: a non-interventional, multi-national, multicentre PASS to assess the long-term safety and tolerability of Odomzo (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC), in order to execute and update the milestones, sample size and execution methods

17.3. Results of PASS imposed in the marketing authorisation(s)⁸³

17.3.1. Ivabradine – CORLENTOR (CAP), IVABRADINE ANPHARM (CAP), PROCORALAN (CAP); NAP - EMEA/H/C-N/PSR/S/0019

Applicants: Anpharm Przedsiębiorstwo Farmaceutyczne (Ivabradine Anpharm), Les Laboratoires Servier (Corlentor, Procolaran), various

PRAC Rapporteur: Menno van der Elst

Scope: Results for a drug utilisation study (DUS) conducted in several European Economic Area (EEA) countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine and adherence to the existing risk minimisation measures

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁸⁴

17.4.1. Atazanavir, atazanavir sulfate - REYATAZ (CAP) - EMEA/H/C/000494/II/0117

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final reports for studies AI424397 (PRINCE I) and AI424451 (PRINCE II) listed as a category 3 studies in the RMP. These studies were phase 3b, prospective, single arm, open-label, international, multicentre studies to evaluate the safety, efficacy and pharmacokinetics of atazanavir powder boosted with ritonavir and administered with an optimised nucleoside reverse transcriptase inhibitor (NRTI) background therapy, in human immunodeficiency virus (HIV) infected paediatric patients. The RMP is updated accordingly (version 15.0). In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

17.4.2. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 006.4

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: Submission of the final results for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)

17.4.3. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 006.4

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

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

⁸⁴ 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

Scope: Submission of the final results for study EP006-401: safety follow-up of severe chronic neutropenia (SCN) patients included in phase 4 study based on data collected via cooperation with the Severe Chronic Neutropenia International Registry and reported annually. Patients were followed-up for a total of five years (one year in the SCN study and four years within the registry)

17.4.4. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0030

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report for study 178-PV-002: a drug utilisation study (DUS) of mirabegron using real-world healthcare databases from Finland, the Netherlands and the United Kingdom (UK) (in fulfilment of post-approval commitment MEA 009.2)

17.4.5. Moroctocog alfa - REFACTO AF (CAP) - EMEA/H/C/000232/II/0147

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study B1831007 (previously referred to as study 3082B2-4435-WW) (listed as a category 3 study in the RMP): a post authorisation safety surveillance registry in previously untreated patients with severe haemophilia A in usual care settings (in fulfilment of post-approval commitment MEA 115)

17.4.6. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0049

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study PZP034AKR02 listed as a category 3 study in the RMP): a non-interventional PASS to monitor the safety and effectiveness of Votrient (pazopanib) in Korea

17.4.7. Pazopanib - VOTRIENT (CAP) - EMEA/H/C/001141/II/0050

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final report for study PZP034A2401 (listed as a category 3 study in the RMP): 'a prospective observational study of real world treatment patterns and treatment outcomes in patients with advanced or metastatic renal cell carcinoma receiving pazopanib'

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

17.5.1. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.5

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.2. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Julie Williams

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.3. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.2

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study 1245.96: an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients with type 2 diabetes mellitus (T2DM) treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors [final report expected in July 2020]

17.5.4. Filgrastim - FILGRASTIM HEXAL (CAP) - EMEA/H/C/000918/MEA 007.4

Applicant: Hexal AG

PRAC Rapporteur: Patrick Batty

Scope: Seventh annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

17.5.5. Filgrastim - ZARZIO (CAP) - EMEA/H/C/000917/MEA 007.4

Applicant: Sandoz GmbH

PRAC Rapporteur: Patrick Batty

Scope: Seventh annual interim result for study EP06-501: a non-interventional, prospective, long-term safety data collection for Filgrastim Hexal and Zarzio (filgrastim) in healthy unrelated stem cell donors undergoing peripheral blood progenitor cell mobilisation (SMART) [final clinical study report (CSR) due date: 31/12/2019]

17.5.6. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 012.7

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Seventh annual interim pooled report for studies D2403 (a long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with MS newly started on fingolimod once daily or treated with another approved disease-modifying therapy), D2404 (multinational Gilenya pregnancy exposure registry in multiple sclerosis (MS)), D2406 (a long-term, prospective, non-interventional, multinational, parallel-cohort study monitoring safety in patients with MS newly initiated on fingolimod once daily or treated with another approved disease-modifying therapy) and study D2409 (a long-term, open-label, multicentre study assessing long-term cardiovascular risks in patients treated with fingolimod). This procedure also includes an annual report for the pregnancy intensive monitoring (PRIM) study

17.5.7. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.5

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third progress report for study MK-8259-013, the ulcerative colitis (UC) Nordic registry: a non-interventional observational longitudinal PASS of Simponi (golimumab) in the treatment of UC using Nordic national health registries

17.5.8. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.9

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Doris Stenver

Scope: MAH's response to MEA 045.8 [fourth annual progress report for diabetes pregnancy registry (NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with insulin detemir in pregnancy women with diabetes mellitus] as per the request for supplementary information (RSI) adopted in April 2018

17.5.9. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/MEA 001.6

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Interim results for study 178-CL-114: a non-imposed, non-interventional, safety long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (individual and composite outcomes) in patients administered mirabegron and other treatments for overactive bladder

17.5.10. Nomegestrol acetate, estradiol - ZOELY (CAP) - EMEA/H/C/001213/ANX 011.4

Applicant: Teva B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Fourth interim report for the prospective observational study to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrel/estradiol users compared with the VTE risk in users of combined oral contraceptives containing levonorgestrel (as imposed in accordance with Article 10(a) of Regulation (EC) No 726/2004

17.5.11. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 005.3

Applicant: Teva B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 005.2 [results of a feasibility assessment conducted in US healthcare databases as per the agreed protocol (final version dated 25 May 2017) for study C38072-AS-50027: a long-term non-interventional cohort study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using secondary administrative healthcare data (listed as category 3 study in the RMP)] as per the request for supplementary information (RSI) adopted in May 2018

17.5.12. Sapropterin - KUVAN (CAP) - EMEA/H/C/000943/MEA 003.8

Applicant: BioMarin International Limited

PRAC Rapporteur: Rhea Fitzgerald

Scope: Seventh interim report for the Kuvan adult maternal paediatric European registry (KAMPER) registry, study EMR700773-001: a non-imposed, non-interventional exploring the long-term safety of Kuvan (sapropterin) use in patients with hyperphenylalaninaemia (HPA) as well as information regarding Kuvan use during pregnancy in women with HPA and data regarding childhood growth and neurocognitive outcomes

17.6. Others

17.6.1. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/MEA 001

Applicant: CSL Behring GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Progress study report for clinical study CSL654-3003 (listed as a category 3 study in the RMP): a phase 3b open-label, multicentre, safety and efficacy extension study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with haemophilia B, including previously untreated patients (PUP)

17.6.2. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 003

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Annika Folin

Scope: Protocol for study CO-338-095 (listed as a category 3 study in the RMP): an in vivo drug-drug interaction (DDI) study with breast cancer resistance protein (BCRP) substrate, a phase 1, open label, DDI study to determine the effect of rucaparib on the pharmacokinetics of rosuvastatin in patients with advanced solid tumours (from initial

opinion/MAA)

17.6.3. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/MEA 004

Applicant: Clovis Oncology UK Limited

PRAC Rapporteur: Annika Folin

Scope: Protocol for study CO-338-095 (listed as a category 3 study in the RMP): an in vivo drug-drug interaction (DDI) study with contraceptives: a phase 1, open label, DDI study to determine the effect of rucaparib on the pharmacokinetics of oral contraceptives in female patients with advanced solid tumours

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. Clofarabine - EVOLTRA (CAP) - EMEA/H/C/000613/S/0059 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ex vivo expanded autologous human corneal epithelial cells containing stem cells - HOLOCLAR (CAP) - EMEA/H/C/002450/R/0021 (with RMP)

Applicant: Chiesi Farmaceutici S.p.A., ATMP⁸⁵

PRAC Rapporteur: Julie Williams

Scope: Conditional renewal of the marketing authorisation

18.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0009 (without RMP)

Applicant: Intercept Pharma Ltd

PRAC Rapporteur: Menno van der Elst

EMA resources: PM: Silvia Domingo Roige; RMS: Nadia Amaouche; EPL: Joachim Musaus

Scope: Conditional renewal of the marketing authorisation

18.2.3. Vandetanib - CAPRELSA (CAP) - EMEA/H/C/002315/R/0032 (without RMP)

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/R/0040 (with RMP)

Applicant: Servier (Ireland) Industries Ltd.

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

18.3.2. Agomelatine - VALDOXAN (CAP) - EMEA/H/C/000915/R/0042 (with RMP)

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Karen Pernille Harg

Scope: 5-year renewal of the marketing authorisation

18.3.3. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/R/0039 (without RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

⁸⁵ Advanced therapy medicinal product

18.3.4. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/R/0024 (without RMP)

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/R/0040 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.6. Indacaterol, glycopyrronium - ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/R/0028 (without RMP)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

18.3.7. Mifamurtide - MEPACT (CAP) - EMEA/H/C/000802/R/0047 (without RMP)

Applicant: Takeda France SAS

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.8. Para-aminosalicylic acid - GRANUPAS (CAP) - EMEA/H/C/002709/R/0026 (without RMP)

Applicant: Eurocept International B.V.

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.9. Pregabalin - PREGABALIN PFIZER (CAP) - EMEA/H/C/003880/R/0025 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: 5-year renewal of the marketing authorisation

18.3.10. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/R/0032 (without RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

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 01-04 October 2018 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
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Andri Andreou	Member	Cyprus	No restrictions applicable to this meeting	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	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	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	3.3.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452
Adrien Inoubli	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final	4.2.2. Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	VELOTAB (CAP); NAP
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	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 discussion, final deliberations and voting on:	3.3.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452 4.3.5. Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestrol acetate - ZOELY (CAP), NAP;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP) 4.3.6. Hormonal contraceptives: Chlormadinone, estradiol (NAP); chlormadinone acetate, ethinylestradiol (NAP); conjugated estrogens, medrogestone (NAP); conjugated estrogens, medroxyprogester

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				one acetate (NAP); conjugated estrogens, norgestrel (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel ,ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, estradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, estriol, levonorgestrel (NAP); estradiol, gestodene (NAP); estradiol, levonorgestrel (NAP); estradiol, medroxyprogesterone acetate (NAP); estradiol, norethisterone (NAP); estradiol, norgestimate (NAP); estradiol (17-beta), progesterone (NAP); estradiol

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(17-beta), trimegestone (NAP); estradiol valerate, norgestrel (NAP); ethinylestradiol, etonogestrel (NAP); ethinylestradiol, etynodiol (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinylestradiol, lynestrenol (NAP); ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); mestranol, norethisterone (NAP); nomegestrol (NAP); nomegestrol acetate, estradiol – ZOELY (CAP); norelgestromin,

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				ethinyl estradiol – EVRA (CAP), NAP; norethisterone (NAP) 6.4.1. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/LEG 038 6.3.6. Ciprofloxacin (NAP) - PSUSA/00000775/201801 11.2.1. Combined hormonal contraceptives (CHCs) containing dienogest and ethinylestradiol (DNG/EE) (NAP) - DE/H/xxxx/WS/534 11.2.2. Finasteride (NAP) - SE/H/xxxx/WS/243
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member - via telephone *	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	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
Jamina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	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 restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Marco Greco	Member	Patients' Organisation Representative	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
			this meeting	
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Katarina Gvozdanović	Expert - via telephone *	Croatia	No interests declared	Full involvement
Barbara Kovačić	Expert - via telephone *	Croatia	No interests declared	Full involvement
Marina Lesičar	Expert - via telephone *	Croatia	No interests declared	Full involvement
Sanja Prpić	Expert - via telephone *	Croatia	No restrictions applicable to this meeting	Full involvement
Jana Šípková	Expert - via telephone *	Czech Republic	No interests declared	Full involvement
Radim Tobolka	Expert - via telephone *	Czech Republic	No interests declared	Full involvement
Ines Messai	Expert - in person*	France	No interests declared	Full involvement
Annabelle Page	Expert - via telephone *	France	No interests declared	Full involvement
Christine Diesinger	Expert - via telephone *	Germany	No interests declared	Full involvement
Maxim Frizler	Expert - via	Germany	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone *		declared	
Thomas Grüger	Expert - via telephone *	Germany	No interests declared	Full involvement
Claudia Kayser	Expert - via telephone *	Germany	No interests declared	Full involvement
Ellen Pantke	Expert - via telephone *	Germany	No restrictions applicable to this meeting	Full involvement
Karin Seifert	Expert - in person*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Emma Lawless	Expert - via telephone *	Ireland	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - via telephone *	Netherlands	No interests declared	Full involvement
Dolores Montero Corominas	Expert - via telephone *	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Bolin	Expert - via telephone *	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - via telephone *	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elina Rönnemaa	Expert - via telephone *	Sweden	No interests declared	Full involvement
Natalie Badoo	Expert - in person*	United Kingdom	No interests declared	Full involvement
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Ross Hawkes	Expert - in person*	United Kingdom	No participation in discussion, final deliberations and voting on:	4.2.2. Olanzapine – ZALASTA (CAP), ZYPADHERA (CAP), ZYPREXA (CAP), ZYPREXA VELOTAB (CAP); NAP 6.2.4. Pemetrexed - ALIMTA (CAP); ARMISARTE (CAP); NAP - PSUSA/00002330/201802
Rory Littlebury	Expert - in person*	United Kingdom	No interests declared	Full involvement
Kiernan Trevett	Expert - in person*	United Kingdom	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/>