



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

11 February 2016  
EMA/PRAC/92676/2016  
Procedure Management and Committees Support Division

## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the PRAC meeting on 11-14 January 2016

Chair: June Raine – Vice-Chair: Almath Spooner

### **Health and safety information**

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

### **Disclaimers**

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

Of note, these 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 ongoing 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).



## Table of contents

<b>1.</b>	<b>Introduction</b>	<b>13</b>
1.1.	Welcome and declarations of interest of members, alternates and experts .....	13
1.2.	Agenda of the meeting on 11-14 January 2016 .....	13
1.3.	Minutes of the previous meeting on 30 November–3 December 2015 .....	13
<b>2.</b>	<b>EU referral procedures for safety reasons: urgent EU procedures</b>	<b>13</b>
2.1.	Newly triggered procedures .....	13
2.2.	Ongoing procedures .....	13
2.3.	Procedures for finalisation.....	14
2.4.	Planned public hearings.....	14
<b>3.</b>	<b>EU referral procedures for safety reasons: other EU referral procedures</b>	<b>14</b>
3.1.	Newly triggered procedures .....	14
3.2.	Ongoing procedures .....	14
3.2.1.	Fusafungine (NAP), nasal and oral solution - EMEA/H/A-31/1420.....	14
3.3.	Procedures for finalisation.....	14
3.3.1.	Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416 .....	14
3.4.	Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request .....	15
3.5.	Others .....	15
<b>4.</b>	<b>Signals assessment and prioritisation</b>	<b>15</b>
4.1.	New signals detected from EU spontaneous reporting systems .....	15
4.1.1.	Cisplatin (NAP) .....	15
4.1.2.	Cytarabine – DEPOCYTE (CAP) .....	16
4.1.3.	Dapagliflozin – FORXIGA (CAP); EDISTRIDE (CAP) dapagliflozin, metformin - XIGDUO (CAP); EBYMECT (CAP).....	17
4.1.4.	Gefitinib – IRESSA (CAP) .....	18
4.1.5.	Levetiracetam (oral solution) – KEPPRA (CAP), NAP .....	19
4.1.6.	Loratadine (NAP) .....	20
4.1.7.	Natalizumab – TYSABRI (CAP).....	21
4.2.	New signals detected from other sources .....	22
4.2.1.	Quinine (NAP) .....	22
4.2.2.	Warfarin (NAP) .....	22
4.3.	Signals follow-up and prioritisation .....	23
4.3.1.	Methotrexate (NAP) .....	23
4.3.2.	Oxybutynin – KENTERA (CAP) - EMEA/H/C/000532/SDA/021 .....	24
4.3.3.	Paracetamol (NAP), phenylephrine (NAP).....	25
4.3.4.	Peginterferon alfa-2a – PEGASYS (CAP) – EMEA/H/C/000395/SDA/055 .....	26

4.3.5.	Recombinant factor VIII: antihemophilic factor (recombinant) (NAP) moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), KOGENATE (CAP) .....	26
4.3.6.	Saxagliptin – ONGLYZA (CAP)- EMEA/H/C/001039/SDA/0039; saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/SDA/016 .....	27
4.3.7.	Thioctic acid (NAP).....	27

## **5. Risk management plans (RMPs) 28**

<b>5.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>28</b>
5.1.1.	Allogeneic T cells genetically modified to express suicide gene - EMEA/H/C/002801, Orphan, ATMP .....	28
5.1.2.	Daratumumab - EMEA/H/C/004077, Orphan .....	28
5.1.3.	Eftrenonacog alfa - EMEA/H/C/004142, Orphan .....	29
5.1.4.	Pandemic influenza vaccine H5N1 (live attenuated, nasal) - EMEA/H/C/003963 .....	29
5.1.5.	Zonisamide - EMEA/H/C/004127.....	29
<b>5.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures.....</b>	<b>29</b>
<b>5.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures .....</b>	<b>29</b>
5.3.1.	Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/II/0079.....	29

## **6. Periodic safety update reports (PSURs) 30**

<b>6.1.</b>	<b>PSUR procedures including centrally authorised products (CAPs) only .....</b>	<b>30</b>
6.1.1.	Azacitidine – VIDAZA (CAP) - PSUSA/00274/201505 (with RMP) .....	30
6.1.2.	Cabazitaxel – JEVTANA (CAP) - PSUSA/00476/201506 .....	31
6.1.3.	Gefitinib – IRESSA (CAP) - PSUSA/01518/201507 .....	32
6.1.4.	Mirabegron – BETMIGA (CAP) - PSUSA/10031/201506 (with RMP).....	33
6.1.5.	Ponatinib – ICLUSIG (CAP) - PSUSA/10128/201506 (with RMP).....	34
6.1.6.	Sofosbuvir – SOVALDI (CAP) - PSUSA/10134/201506 (with RMP) .....	34
6.1.7.	Trametinib – MEKINIST (CAP) - PSUSA/10262/201505.....	35
6.1.8.	Umeclidinium bromide, vilanterol – ANORO (CAP), LAVENTAIR (CAP) - PSUSA/10264/201506.....	36
<b>6.2.</b>	<b>PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>37</b>
6.2.1.	Topotecan – HYCAMTIN (CAP), POTACTASOL (CAP), TOPOTECAN ACTAVIS (CAP), TOPOTECAN HOSPIRA (CAP), TOPOTECAN TEVA (CAP), NAP - PSUSA/02997/201505 .....	37
<b>6.3.</b>	<b>PSUR procedures including nationally authorised products (NAPs) only .....</b>	<b>38</b>
6.3.1.	Apomorphine (NAP) - PSUSA/00000227/201505 .....	38
6.3.2.	Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201505 .....	40
6.3.3.	Gadobenic acid (NAP) - PSUSA/00001500/201504.....	41
6.3.4.	Gadobutrol (NAP) - PSUSA/00001502/201504 .....	41
6.3.5.	Gadodiamide (NAP) - PSUSA/00001503/201504.....	42
6.3.6.	Gadopentetic acid (NAP) - PSUSA/00001504/201504.....	43

6.3.7.	Gadoteric acid (intravenous and intravascular formulations) (NAP) - PSUSA/00001506/201504 .....	44
6.3.8.	Gadoteridol (NAP) - PSUSA/00001507/201504 .....	45
6.3.9.	Gadoxetic acid disodium (NAP) - PSUSA/00001509/201504 .....	46
6.3.10.	Iodine ( <sup>131</sup> I) iobenguane (NAP) - PSUSA/00001764/201505 .....	46
6.3.11.	Isotretinoin (NAP) - PSUSA/00001795/201505 .....	47
6.3.12.	Milnacipran (NAP) - PSUSA/00002063/201504 .....	48
6.3.13.	Oxaliplatin (NAP) - PSUSA/00002229/201504 .....	49
6.3.14.	Pamidronate (NAP) - PSUSA/00002269/201505 .....	50
6.3.15.	Ticlopidine (NAP) - PSUSA/00002952/201505 .....	51
<b>6.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>52</b>
6.4.1.	Gadoversetamide – OPTIMARK (CAP) - EMEA/H/C/000745/LEG 025.....	52
<b>7.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>53</b>
<b>7.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>53</b>
7.1.1.	Chlormadinone acetate, ethinyl estradiol (NAP) – EMEA/H/N/PSP/j/0012.3 .....	53
7.1.2.	Valproate (NAP) - EMEA/H/N/PSP/j/0029.1 .....	53
<b>7.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>54</b>
7.2.1.	Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/MEA/015 .....	54
<b>7.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s).....</b>	<b>55</b>
<b>7.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s).....</b>	<b>56</b>
7.4.1.	Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0807 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0807 (without RMP).....	56
<b>7.5.</b>	<b>Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....</b>	<b>57</b>
<b>7.6.</b>	<b>Others .....</b>	<b>57</b>
<b>7.7.</b>	<b>New Scientific Advice .....</b>	<b>57</b>
<b>7.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>57</b>
<b>7.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>57</b>
<b>8.</b>	<b>Renewals of the marketing authorisation, conditional renewal and annual reassessments .....</b>	<b>57</b>
<b>8.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>57</b>
<b>8.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>57</b>
<b>8.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>58</b>
<b>9.</b>	<b>Product related pharmacovigilance inspections .....</b>	<b>58</b>
<b>9.1.</b>	<b>List of planned pharmacovigilance inspections.....</b>	<b>58</b>
<b>9.2.</b>	<b>Ongoing or concluded pharmacovigilance inspections.....</b>	<b>58</b>
<b>10.</b>	<b>Other safety issues for discussion requested by the CHMP or the EMA .....</b>	<b>58</b>
<b>10.1.</b>	<b>Safety related variations of the marketing authorisation.....</b>	<b>58</b>

10.1.1.	Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0792 elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/WS/0792 emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/WS/0792 emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0792 emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0792 tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0792.....	58
<b>10.2.</b>	<b>Timing and message content in relation to Member States’ safety announcements</b> .....	<b>59</b>
<b>10.3.</b>	<b>Other requests.....</b>	<b>59</b>
10.3.1.	Human thrombin – FLOSEAL HAEMOSTATIC MATRIX (FLOSEAL V/H SD) (medical device); HEMOBLAST HAEMOSTATIC AGENT (medical device); SURGIFLO HAEMOSTATIC MATRIX KIT (medical device).....	59
<b>11.</b>	<b>Other safety issues for discussion requested by the Member States</b>	<b>60</b>
<b>11.1.</b>	<b>Safety related variations of the marketing authorisation.....</b>	<b>60</b>
11.1.1.	Cyproterone acetate, ethinylestradiol (NAP) - NL/H/xxxx/WS/150 .....	60
<b>11.2.</b>	<b>Other requests.....</b>	<b>61</b>
<b>12.</b>	<b>Organisational, regulatory and methodological matters</b>	<b>61</b>
<b>12.1.</b>	<b>Mandate and organisation of the PRAC.....</b>	<b>61</b>
<b>12.2.</b>	<b>Coordination with EMA Scientific Committees or CMDh .....</b>	<b>61</b>
12.2.1.	Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population.....	61
12.2.2.	Paediatric Committee (PDCO) - paediatric pharmacovigilance: organ maturation tables....	61
<b>12.3.</b>	<b>Coordination with EMA Working Parties/Working Groups/Drafting Groups .....</b>	<b>62</b>
12.3.1.	Advisory group on classification of post-authorisation studies (CPAS) to the marketing authorisations .....	62
12.3.2.	Guideline on safety and efficacy follow-up – risk management plans for ATMPs .....	62
<b>12.4.</b>	<b>Cooperation within the EU regulatory network .....</b>	<b>62</b>
12.4.1.	EMA review of seasonal influenza vaccines enhanced safety surveillance systems .....	62
12.4.2.	EMA reflection paper on extrapolation across age groups .....	62
<b>12.5.</b>	<b>Cooperation with International Regulators.....</b>	<b>63</b>
<b>12.6.</b>	<b>Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee .....</b>	<b>63</b>
<b>12.7.</b>	<b>PRAC work plan .....</b>	<b>63</b>
12.7.1.	PRAC work plan 2016.....	63
<b>12.8.</b>	<b>Planning and reporting .....</b>	<b>63</b>
<b>12.9.</b>	<b>Pharmacovigilance audits and inspections .....</b>	<b>63</b>
12.9.1.	Pharmacovigilance systems and their quality systems .....	63
12.9.2.	Pharmacovigilance inspections .....	63
12.9.3.	Pharmacovigilance audits.....	63
<b>12.10.</b>	<b>Periodic safety update reports (PSURs) &amp; Union reference date (EURD) list .....</b>	<b>64</b>

12.10.1.	Periodic safety update reports .....	64
12.10.2.	Granularity and Periodicity Advisory Group (GPAG) .....	64
12.10.3.	PSUR action group - roadmap for PSUR issues: scoping paper as a basis for the workshop in January 2016 .....	64
12.10.4.	PSUR/PSUSA – guidance on handling of EU single PSUR procedures for suspended or withdrawn/non-renewed/revoked marketing authorisations .....	64
12.10.5.	PSURs repository – update on post-audit requirements .....	64
12.10.6.	Union reference date list – consultation on the draft list .....	64
<b>12.11.</b>	<b>Signal management .....</b>	<b>65</b>
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group .....	65
<b>12.12.</b>	<b>Adverse drug reactions reporting and additional reporting .....</b>	<b>65</b>
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	65
12.12.2.	Additional monitoring .....	65
12.12.3.	List of products under additional monitoring – consultation on the draft list .....	65
<b>12.13.</b>	<b>EudraVigilance database.....</b>	<b>66</b>
12.13.1.	Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project update .....	66
<b>12.14.</b>	<b>Risk management plans and effectiveness of risk minimisations.....</b>	<b>66</b>
12.14.1.	Risk management systems - Summaries of risk management plans (RMP): update.....	66
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations .....	67
<b>12.15.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>67</b>
12.15.1.	Post-authorisation Safety Studies – imposed PASS .....	67
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS .....	67
<b>12.16.</b>	<b>Community procedures.....</b>	<b>67</b>
12.16.1.	Referral procedures for safety reasons .....	67
<b>12.17.</b>	<b>Renewals, conditional renewals, annual reassessments .....</b>	<b>67</b>
<b>12.18.</b>	<b>Risk communication and transparency .....</b>	<b>67</b>
12.18.1.	Public participation in pharmacovigilance .....	67
12.18.2.	Safety communication .....	67
<b>12.19.</b>	<b>Continuous pharmacovigilance .....</b>	<b>67</b>
12.19.1.	Incident management .....	67
<b>12.20.</b>	<b>Others .....</b>	<b>67</b>
12.20.1.	Initial marketing authorisation(s) - revised accelerated assessment procedural timetables	67
12.20.2.	Pharmacovigilance operation and implementation - proposal for a streamlined governance structure .....	68
12.20.3.	Strategy on measuring the impact of pharmacovigilance activities .....	68
<b>13.</b>	<b>Any other business .....</b>	<b>68</b>
<b>14.</b>	<b>Annex I – Risk management plans .....</b>	<b>69</b>
<b>14.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>69</b>

14.1.1.	Amlodipine, valsartan - EMEA/H/C/004037 .....	69
14.1.2.	Atazanavir - EMEA/H/C/004048 .....	69
14.1.3.	Bortezomib - EMEA/H/C/004076.....	69
14.1.4.	Selexipag - EMEA/H/C/003774, Orphan.....	69
<b>14.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedure .....</b>	<b>69</b>
14.2.1.	Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0771 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0771.....	69
14.2.2.	Colistimethate sodium – COLOBREATHE (CAP) - EMEA/H/C/001225/II/0021 .....	69
14.2.3.	Imatinib – GLIVEC (CAP) - EMEA/H/C/000406/II/0098/G .....	70
14.2.4.	Piperaquine tetraphosphate, arteminol – EURARTESIM (CAP) - EMEA/H/C/001199/II/002070	
14.2.5.	Teriparatide – FORSTEO (CAP) - EMEA/H/C/000425/II/0042/G .....	70
<b>14.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedure.....</b>	<b>70</b>
14.3.1.	Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0845 lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0845 lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0845.....	70
14.3.2.	Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/II/0036/G.....	71
14.3.3.	Atazanavir, atazanavir sulfate – REYATAZ (CAP) - EMEA/H/C/000494/X/0094/G .....	71
14.3.4.	Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0016/G .....	71
14.3.5.	Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0089 .....	71
14.3.6.	Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/II/0045 .....	72
14.3.7.	Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/X/0043.....	72
14.3.8.	Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/X/0022/G .....	72
14.3.9.	Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0029/G.....	72
14.3.10.	Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0030 .....	72
14.3.11.	Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/II/0021 .....	73
14.3.12.	Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0016.....	73
14.3.13.	Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0017 .....	73
14.3.14.	Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/II/0017 .....	73
14.3.15.	Insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/II/0012 .....	73
14.3.16.	Nintedanib – OFEV (CAP) - EMEA/H/C/003821/WS/0766; VARGATEF (CAP) - EMEA/H/C/002569/WS/0766.....	74
14.3.17.	Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0002 .....	74
14.3.18.	Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0003 .....	74
14.3.19.	Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0008 .....	74
14.3.20.	Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/II/0028 .....	74
14.3.21.	Ranibizumab – LUCENTIS (CAP) - EMEA/H/C/000715/II/0059 .....	75
14.3.22.	Safinamide – XADAGO (CAP) - EMEA/H/C/002396/II/0008 .....	75
14.3.23.	Simeprevir – OLYSIO (CAP) - EMEA/H/C/002777/II/0015 .....	75

14.3.24.	Sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/WS/0846; RISTABEN (CAP) - EMEA/H/C/001234/WS/0846; TESAVEL (CAP) - EMEA/H/C/000910/WS/0846; XELEVIA (CAP) - EMEA/H/C/000762/WS/0846 .....	75
14.3.25.	Sitagliptin, metformin hydrochloride – EFFICIB (CAP) - EMEA/H/C/000896/WS/0847; JANUMET (CAP) - EMEA/H/C/000861/WS/0847; RISTFOR (CAP) - EMEA/H/C/001235/WS/0847; VELMETIA (CAP) - EMEA/H/C/000862/WS/0847 .....	75
14.3.26.	Sonidegib – ODOMZO (CAP) - EMEA/H/C/002839/II/0001/G .....	76
14.3.27.	Telavancin – VIBATIV (CAP) - EMEA/H/C/001240/II/0023 .....	76
14.3.28.	Ulipristal – ESMYA (CAP) - EMEA/H/C/002041/II/0037 .....	76
14.3.29.	Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0029 .....	76
14.3.30.	Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0030 .....	76
14.3.31.	Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0031/G .....	76

## **15. ANNEX I - Periodic safety update reports (PSURs) 77**

<b>15.1.</b>	<b>PSUR procedures including centrally authorised products only .....</b>	<b>77</b>
15.1.1.	Afamelanotide – SCENESSE (CAP) - PSUSA/10314/201506 .....	77
15.1.2.	Ambrisentan – VOLIBRIS (CAP) - PSUSA/00129/201506 .....	77
15.1.3.	Avanafil – SPEDRA (CAP) - PSUSA/10066/201506 .....	77
15.1.4.	Belatacept – NULOJIX (CAP) - PSUSA/00311/201506 .....	77
15.1.5.	Brimonidine tartrate, brinzolamide – SIMBRINZA (CAP) - PSUSA/10273/201506 .....	78
15.1.6.	Bromfenac – YELLOX (CAP) - PSUSA/00436/201505 .....	78
15.1.7.	C1-esterase inhibitor, human – CINRYZE (CAP) - PSUSA/10104/201506 .....	78
15.1.8.	Canakinumab – ILARIS (CAP) - PSUSA/00526/201506 (with RMP) .....	78
15.1.9.	Daclatasvir – DAKLINZA (CAP) - PSUSA/10295/201507 .....	78
15.1.10.	Dasatinib – SPRYCEL (CAP) - PSUSA/00935/201506 .....	78
15.1.11.	Dextromethorphan hydrobromide, quinidine sulfate – NUEDEXTA (CAP) - PSUSA/10089/201506 .....	78
15.1.12.	Galsulfase – NAGLAZYME (CAP) - PSUSA/01515/201505 .....	79
15.1.13.	Human fibrinogen, human thrombin – EVARREST (CAP), EVICEL (CAP), RAPLIXA (CAP), TACHOSIL (CAP) - PSUSA/10297/201506 .....	79
15.1.14.	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP) - PSUSA/01634/201505 .....	79
15.1.15.	Hydroxycarbamide – SIKLOS (CAP) - PSUSA/01692/201506 (with RMP) .....	79
15.1.16.	Imiglucerase – CEREZYME (CAP) - PSUSA/01727/201505 .....	79
15.1.17.	Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - PSUSA/01742/20150679	
15.1.18.	Liraglutide – SAXENDA (CAP), VICTOZA (CAP) - PSUSA/01892/201506 .....	79
15.1.19.	Matrix applied characterised autologous cultured chondrocytes – MACI (CAP) - PSUSA/10116/201506 .....	80
15.1.20.	Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - PSUSA/10296/201505 .....	80
15.1.21.	Nepafenac – NEVANAC (CAP) - PSUSA/02143/201505 .....	80
15.1.22.	Nivolumab – NIVOLUMAB BMS (CAP), OPDIVO (CAP) - PSUSA/10379/201507 .....	80



15.1.23.	Nonacog gamma – RIXUBIS (CAP) - PSUSA/10320/201506 .....	80
15.1.24.	Olaparib – LYNPARZA (CAP) - PSUSA/10322/201506 .....	80
15.1.25.	Paliperidone – INVEGA (CAP), PALIPERIDONE JANSSEN (CAP), XEPLION (CAP) - PSUSA/02266/201506 (with RMP) .....	80
15.1.26.	Pegaptanib – MACUGEN (CAP) - PSUSA/02324/201506 .....	81
15.1.27.	Pegloticase – KRYSTEXXA (CAP) - PSUSA/10046/201507 .....	81
15.1.28.	Pertuzumab – PERJETA (CAP) - PSUSA/10125/201506 .....	81
15.1.29.	Secukinumab – COSENTYX (CAP) - PSUSA/10341/201506.....	81
15.1.30.	Sildenafil – REVATIO (CAP) - PSUSA/02700/201505 .....	81
15.1.31.	Tobramycin – TOBI PODHALER (CAP) - PSUSA/09315/201506 .....	81
<b>15.2.</b>	<b>PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>81</b>
15.2.1.	Aminolevulinic acid – AMELUZ (CAP), NAP - PSUSA/10006/201506.....	81
15.2.2.	Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP), NAP - PSUSA/01633/201505 .....	82
15.2.3.	Imatinib – GLIVEC (CAP), NAP - PSUSA/01725/201505 .....	82
15.2.4.	Measles, mumps and rubella vaccine (live) – M-M-RVAXPRO (CAP), NAP - PSUSA/01937/201505.....	82
15.2.5.	Nevirapine – VIRAMUNE (CAP), NAP - PSUSA/02147/201505 .....	82
15.2.6.	Nitric oxide – INOMAX (CAP), NAP - PSUSA/02172/201506.....	82
15.2.7.	Olopatadine – OPATANOL (CAP), NAP - PSUSA/02211/201504 .....	82
<b>15.3.</b>	<b>PSUR procedures including nationally approved products (NAPs) only .....</b>	<b>83</b>
15.3.1.	Ceftriaxone (NAP) - PSUSA/00000613/201505 .....	83
15.3.2.	Cefuroxime sodium (for intracameral use) (NAP) - PSUSA/00010206/201505 .....	83
15.3.3.	Clevidipine (NAP) - PSUSA/00010288/201505 .....	83
15.3.4.	Clotiazepam (NAP) - PSUSA/00000827/201505.....	83
15.3.5.	Diphtheria, tetanus vaccines (adsorbed) (NAP) - PSUSA/00001128/201505.....	83
15.3.6.	Fentanyl (transdermal patches, solution for injection) (NAP) - PSUSA/00001370/201504 .	83
15.3.7.	Flunarizine (NAP) - PSUSA/00001416/201505 .....	83
15.3.8.	5 fluorouracil, salicylic acid (NAP) - PSUSA/00000008/201505 .....	84
15.3.9.	Gadoteric acid (intra-articular formulation) (NAP) - PSUSA/00001505/201504 .....	84
15.3.10.	Misoprostol (gynaecological indication, - induction of labour) (NAP) - PSUSA/00010353/201505 .....	84
15.3.11.	Misoprostol (gynaecological indication - termination of pregnancy) (NAP) - PSUSA/00010354/201505 .....	84
15.3.12.	Nicergoline (NAP) - PSUSA/00002150/201505 .....	84
15.3.13.	Pholcodine (NAP) - PSUSA/00002396/201505 .....	84
15.3.14.	Praziquantel (NAP) - PSUSA/00002503/201504.....	84
15.3.15.	Ranitidine (NAP) - PSUSA/00002610/201505 .....	85
15.3.16.	Tafloprost (NAP) - PSUSA/00002843/201504.....	85

15.3.17.	Tamoxifen (NAP) - PSUSA/00002846/201504 .....	85
15.3.18.	Terlipressin (NAP) - PSUSA/00002905/201504.....	85
15.3.19.	Thiamphenicol (NAP) - PSUSA/00002925/201505.....	85
<b>15.4.</b>	<b>Follow-up to PSUR procedures.....</b>	<b>85</b>
15.4.1.	Leflunomide – LEFLUNOMIDE MEDAC (CAP) - EMEA/H/C/001227/LEG 011.....	85
15.4.2.	Omalizumab – XOLAIR (CAP) - EMEA/H/C/000606/LEG 050.....	85
15.4.3.	Peginterferon beta-1a – PLEGRIDY (CAP) - EMEA/H/C/002827/LEG 007 .....	86
<b>16.</b>	<b>Annex I – Post-authorisation safety studies (PASS) .....</b>	<b>86</b>
<b>16.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>86</b>
16.1.1.	Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/PSP/0032 .....	86
16.1.2.	Domperidone (NAP) - EMEA/H/N/PSP/j/0016.2.....	86
16.1.3.	Domperidone (NAP) - EMEA/H/N/PSP/j/0031 .....	86
16.1.4.	Idebenone – RAXONE (CAP) - EMEA/H/C/PSP/0034 .....	87
16.1.5.	Ospemifene – SENSHIO (CAP) - EMEA/H/C/PSP/0023.2 .....	87
<b>16.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>87</b>
16.2.1.	Aflibercept – ZALTRAP (CAP) - EMEA/H/C/002532/MEA/002.3.....	87
16.2.2.	Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/MEA/026.1; VALDOXAN (CAP) - EMEA/H/C/000915/MEA/026.1 .....	87
16.2.3.	Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP) - EMEA/H/C/002246/MEA/003.3 .....	87
16.2.4.	Buprenorphine, naloxone – SUBOXONE (CAP) - EMEA/H/C/000697/MEA/023.5 .....	88
16.2.5.	Cobicistat – TYBOST (CAP) - EMEA/H/C/002572/MEA/012.2.....	88
16.2.6.	Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/MEA/027.1 .....	88
16.2.7.	Filgrastim – NIVESTIM (CAP) - EMEA/H/C/001142/MEA/015 .....	88
16.2.8.	Flutemetamol ( <sup>18</sup> F) – VIZAMYL (CAP) - EMEA/H/C/002557/MEA/003.2 .....	88
16.2.9.	Human normal immunoglobulin – PRIVIGEN (CAP) - EMEA/H/C/000831/MEA/022.3 .....	89
16.2.10.	Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/MEA/023.2 .....	89
16.2.11.	Meningococcal group b vaccine (rDNA, component, adsorbed) – BEXSERO (CAP) - EMEA/H/C/002333/MEA/017 .....	89
16.2.12.	Safinamide – XADAGO (CAP) - EMEA/H/C/002396/MEA/004 .....	89
16.2.13.	Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/MEA/021.....	89
16.2.14.	Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/013.1 .....	89
16.2.15.	Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/014.....	90
<b>16.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s).....</b>	<b>90</b>
<b>16.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s).....</b>	<b>90</b>
16.4.1.	Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0769 lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/WS/0769, LAMIVUDINE VIIV (Art 58) - EMEA/H/W/000673/WS/0769 lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0769 lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0769 lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/WS/0769 (without RMP) .....	90

16.4.2.	Catridecacog – NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0012/G .....	90
16.4.3.	Eptacog alfa – NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0089 (with RMP).....	91
16.4.4.	Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/II/0073 (with RMP).....	91
16.4.5.	Telaprevir – INCIVO (CAP) - EMEA/H/C/002313/II/0039.....	91
16.4.6.	Vildagliptin – GALVUS (CAP) - EMEA/H/C/000771/WS/0791, JALRA (CAP) - EMEA/H/C/001048/WS/0791, XILIARX (CAP) - EMEA/H/C/001051/WS/0791 Vildagliptin / metformin hydrochloride – EUCREAS (CAP) - EMEA/H/C/000807/WS/0791, ICANDRA (CAP) - EMEA/H/C/001050/WS/0791, ZOMARIST (CAP) - EMEA/H/C/001049/WS/0791 (with RMP) .....	91
<b>16.5.</b>	<b>Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....</b>	<b>91</b>
16.5.1.	Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/MEA/003.3 .....	91
16.5.2.	Indacaterol, glycopyrronium bromide – ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/MEA/004.2 .....	92
16.5.3.	Indacaterol, glycopyrronium bromide – XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/MEA/003.3 .....	92
16.5.4.	Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA/089.12.....	92
16.5.5.	Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA/121.8 .....	92
16.5.6.	Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/004.4 .....	92
16.5.7.	Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/006.3 .....	93
16.5.8.	Influenza vaccine (split virion, inactivated) – IDFLU (CAP) - EMEA/H/C/000966/MEA/032.2; INTANZA (CAP) - EMEA/H/C/000957/MEA/032.2 .....	93
16.5.9.	Nomegestrol, estradiol – ZOELY (CAP) - EMEA/H/C/001213/ANX/011.1.....	93
16.5.10.	Temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/LEG/031.3 .....	93
16.5.11.	Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/256.5 .....	93
16.5.12.	Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/272.....	93
<b>16.6.</b>	<b>Others .....</b>	<b>94</b>
16.6.1.	Rivastigmine – EXELON (CAP) - EMEA/H/C/000169/MEA 036.1, PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.1.....	94

## **17. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments 94**

<b>17.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>94</b>
17.1.1.	Mecasermin – INCRELEX (CAP) - EMEA/H/C/000704/S/0035 (without RMP).....	94
17.1.2.	Tafamidis – VYNDALM (CAP) - EMEA/H/C/002294/S/0031 (without RMP).....	94
<b>17.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>94</b>
17.2.1.	Ceritinib – ZYKADIA (CAP) - EMEA/H/C/003819/R/0004 (without RMP) .....	94
17.2.2.	Delamanid – DELTYBA (CAP) - EMEA/H/C/002552/R/0010 (without RMP).....	95
17.2.3.	Pixantrone dimaleate – PIXUVRI (CAP) - EMEA/H/C/002055/R/0025 (with RMP).....	95
<b>17.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>95</b>

17.3.1.	C1 esterase inhibitor, human – CINRYZE (CAP) - EMEA/H/C/001207/R/0040 (without RMP) .....	95
17.3.2.	Denosumab – XGEVA (CAP) - EMEA/H/C/002173/R/0042 (with RMP) .....	95
17.3.3.	Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/R/0035 (with RMP) .....	95
17.3.4.	Linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/R/0021 (without RMP) .....	95

<b>18.</b>	<b>Annex II – List of participants</b>	<b>95</b>
<b>19.</b>	<b>Annex III - List of acronyms and abbreviations</b>	<b>99</b>
<b>20.</b>	<b>Explanatory notes</b>	<b>99</b>

## 1. Introduction

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

The Chairperson opened the 11-14 January 2016 meeting by welcoming all participants.

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

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

The PRAC Chair welcomed Zane Stade, as the new alternate for Latvia. In addition, the PRAC welcomed the new Dutch presidency of the Council of the EU.

### 1.2. Agenda of the meeting on 11-14 January 2016

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

### 1.3. Minutes of the previous meeting on 30 November–3 December 2015

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 30 November-3 December 2015 were published on the EMA website on 3 February 2016 ([EMA/PRAC/75116/2016](#)).

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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

### 2.3. Procedures for finalisation

None

### 2.4. Planned public hearings

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

#### 3.2.1. Fusafungine (NAP), nasal and oral solution - EMEA/H/A-31/1420

---

Applicant: Les Laboratoires Servier, various

PRAC Rapporteur: Julia Pallos; PRAC Co-rapporteur: Jana Mladá

Scope: Review of the benefit-risk balance following notification by Italy 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 fusafungine-containing products to review the benefit risk of fusafungine following an increase in the reporting rate of serious allergic reactions including anaphylactic reactions in paediatric and adult populations, as well as its potential role in promoting antibiotic resistance. For background information, see [PRAC minutes September 2015](#) and [PRAC minutes January 2016](#).

#### Summary of recommendation(s)/conclusions

The PRAC endorsed the list of experts for the Scientific Advisory Group in Anti-infectives (SAG-AI) organised on 21 January 2016. As a consequence, the Committee adopted a refined list of questions for the SAG-AI.

### 3.3. Procedures for finalisation

#### 3.3.1. Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416

---

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Carmela Macchiarulo

Scope: Review of the benefit-risk balance following notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

#### Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 is ongoing for Tysabri (natalizumab) to review the risk estimates and diagnosis of progressive multifocal leukoencephalopathy (PML) before the development of clinical symptoms and anti-JCV (John Cunningham virus) antibodies in the light of further evidence and scientific progress, in order to better define the risk of PML and identify measures to further minimise it. For background information, see [PRAC minutes May 2015](#), [PRAC minutes September 2015](#), [PRAC minutes October 2015](#), [PRAC minutes November 2015](#) and [PRAC minutes December 2015](#).

#### **Summary of recommendation(s)/conclusions**

Based on the review of the data, and following an oral explanation by the MAH addressing questions from the PRAC, the PRAC adopted a third list of outstanding issues (LoOI) to the MAH including a request for a Direct Healthcare Professional Communication (DHPC). The Committee also adopted a revised timetable for the procedure ([EMA/PRAC/293314/2015 rev4](#)).

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

None

### **3.5. Others**

None

## **4. Signals assessment and prioritisation<sup>1</sup>**

### **4.1. New signals detected from EU spontaneous reporting systems**

#### **4.1.1. Cisplatin (NAP)**

---

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of peripheral arterial thromboembolic events (ATEs) and arterial occlusion  
EPITT 18560 – New signal  
Lead Member State: DK

#### **Background**

Cisplatin is a chemotherapy drug indicated for the treatment of extensive or metastatic tumours such as testicular carcinoma, ovarian carcinoma, squamous cell carcinoma of the head and neck, bladder carcinoma, small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).

During routine signal detection activities, a signal of peripheral arterial thromboembolic events (ATEs) and arterial occlusion was identified by the Netherlands, based on 16 cases

---

<sup>1</sup> 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

retrieved from the Netherlands Pharmacovigilance centre (Lareb) database. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the evidence from case reports in the Netherlands Pharmacovigilance Centre Lareb database, EudraVigilance and the scientific literature. Taking into account that a temporal association between cisplatin exposure and the development of ATEs has been reported in the scientific literature, the PRAC considered that the originator/market lead MAHs should provide a cumulative review of all the cases of peripheral ATEs and arterial occlusion associated with cisplatin.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

### **Summary of recommendation(s)**

- The MAHs (Ebewe Pharma and Pfizer/Pharmacia) should submit to the EMA, within 60 days, a cumulative review of all the cases of peripheral ATEs and arterial occlusion associated with cisplatin. This analysis should include a review of the published literature as well as data from spontaneous reports and reports from studies. The plausible underlying pharmacological mechanism should be discussed. The MAHs should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.2. Cytarabine – DEPOCYTE (CAP)**

---

Applicant: Pacira Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of benign intracranial hypertension

EPITT 18533 – New signal

Lead Member State: UK

### **Background**

Cytarabine is a cell-cycle phase specific antineoplastic agent indicated for the intrathecal treatment of lymphomatous meningitis.

The exposure for Depocyte, a centrally authorised medicine containing cytarabine, is estimated to have been more than 31,819 patients worldwide, in the period from first authorisation in 2001 until March 2015.

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

### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and in the medical literature. Taking into account that all of the cases were well defined and that intracranial hypertension is associated with exposure to cytarabine in the literature, the PRAC considered that the MAH for Depocyte should provide a cumulative review and



detailed analysis of all cases of benign intracranial hypertension associated with use of liposomal intrathecal cytarabine and intrathecal cytarabine from all sources (spontaneous post-marketing reports, clinical and observational studies, scientific literature) using the relevant terms (including benign intracranial hypertension and intracranial pressure increased) and related terms that may be indicative of cases (e.g. papilloedema).

#### **Summary of recommendation(s)**

- The MAH for Depocyte (cytarabine) should submit to the EMA, within 60 days, a cumulative review and detailed analysis of all cases of benign intracranial hypertension associated with use of liposomal intrathecal cytarabine and intrathecal cytarabine from all sources using the relevant terms and related terms that may be indicative of cases. The MAH should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.3. Dapagliflozin – FORXIGA (CAP); EDISTRIDE (CAP) dapagliflozin, metformin - XIGDUO (CAP); EBYMECT (CAP)**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of pancreatitis

EPITT 18558 – New signal

Lead Member State: SE

#### **Background**

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

The post-marketing exposure for Forxiga, a centrally authorised medicine containing dapagliflozin, is estimated to have been more than 121,119 patient-years worldwide, in the period from first authorisation in 2012 until October 2014. The post-marketing exposure for Xigduo, a centrally authorised medicine containing dapagliflozin and metformin, is estimated to have been more than 41,169 patient-years worldwide, in the period from first authorisation in 2014 until July 2015.

During routine signal detection activities, a signal of pancreatitis was identified by the EMA, based on 12 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

The PRAC discussed the 12 cases retrieved from EudraVigilance, including 5 cases with a plausible causality association with dapagliflozin, although some of them occurred in patients with risk factors for pancreatitis. In these 5 cases, a temporal relationship was shown. 3 cases reported a positive de-challenge and one a positive re-challenge, although with some uncertainties as this case was poorly documented. In 4 cases, patients required hospitalisation. All 5 cases were reported as serious, but one symptom-free pancreatitis could be classified as non-serious. In addition, there were 7 cases where causality could not

be ruled out, despite being poorly documented cases. Taking into account that type 2 diabetes is associated with an increased risk of developing pancreatitis and the fact that some of the cases had additional risks or confounding factors, the time-to-onset and a potential positive de/re-challenge in several (at least five) of the cases strengthened the likelihood of a causal relationship between treatment with dapagliflozin and (acute) pancreatitis.

#### **Summary of recommendation(s)**

- The MAH for Forxigo/Edistride (dapagliflozin) and Xigduo/Ebymect (dapagliflozin/metformin) should submit to the EMA, within 60 days, a cumulative review of cases of pancreatitis, including spontaneous cases, cases from clinical trials and the literature. The MAH should also provide a detailed analysis relating to a possible effect of dapagliflozin on the pancreas reflected by increased levels of lipase and amylase, by presenting laboratory values from relevant clinical trials. The MAH should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of the review of cases of pancreatitis leading to a further PRAC recommendation.

#### **4.1.4. Gefitinib – IRESSA (CAP)**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of pneumatosis intestinalis

EPITT 18575 – New signal

Lead Member State: SE

#### **Background**

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

The post-marketing exposure for Iressa, a centrally authorised medicine containing gefitinib, is estimated to have been more than 243,631 patient-years worldwide, in the period from first authorisation in 2009 until July 2015.

During routine signal detection activities, a signal of pneumatosis intestinalis was identified by the EMA, based on 14 supportive cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and from the literature. Taking into account that pneumatosis intestinalis, being a radiological finding, may be a sign of a serious and potentially life-threatening condition, and that a number of cases of positive de-challenge and/or re-challenge were reported where an involvement of gefitinib cannot be ruled out, the PRAC agreed that the MAH for Iressa should submit a cumulative review of all the cases of pneumatosis intestinalis associated with gefitinib.

### **Summary of recommendation(s)**

- The MAH for Iressa (gefitinib) should submit to the EMA, within 60 days, a cumulative review of all the cases of pneumatosis intestinalis associated with gefitinib. This analysis should include a review of the published literature as well as data from spontaneous reports and reports from studies. The MAH should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.5. Levetiracetam (oral solution) – KEPBRA (CAP), NAP**

---

Applicant: UCB Pharma SA

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of medication errors associated with accidental overdoses

EPITT 10519 – New signal

Lead Member State: BE

### **Background**

Levetiracetam is a pyrrolidone derivative indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. As an adjunctive treatment, levetiracetam is indicated for the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy; for the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy as well as for the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

The exposure for Keppra, a centrally authorised medicine containing levetiracetam, is estimated to have been more than 6,052,842 patient-years worldwide, in the period from first authorisation in 2000 until November 2012.

During routine signal detection activities, the MAH for Keppra (levetiracetam) identified in its Pharmacovigilance database 27 new cases of medication errors leading to accidental overdoses of levetiracetam oral solutions, and brought this signal to the attention of the EMA. Two third of the cases occurred in the EU, all had a favourable outcome. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the safety signal assessment provided by the MAH as well as the cases of overdose and accidental overdose and medication errors retrieved from EudraVigilance as well as data from the published literature. Having considered the available evidence, the PRAC agreed that the MAH for Keppra should submit responses to a list of questions and discuss the need for any potential amendment to the product information, external packaging and/or the risk management plan accordingly.

### **Summary of recommendation(s)**

- The MAH for Keppra (levetiracetam) should submit to the EMA, within 60 days, responses to a list of questions on the root cause analysis for the medication errors, the readability of the package leaflet, the need to improve the package leaflet and the information in the outer packaging, and the need to include the age range on the syringe. The MAH should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.1.6. Loratadine (NAP)

---

Applicant: various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of QT prolongation and Torsade de Pointe

EPITT 18576 – New signal

Lead Member State: BE

#### **Background**

Loratadine is a second-generation peripheral histamine H1-receptor antagonist indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

Following the publication of the article by *Poluzzi E. et al.*<sup>2</sup>, a signal of QT prolongation and Torsade de Pointe was identified by Belgium, based on 9 supportive cases of electrocardiogram QT prolonged and 5 supportive cases of torsades de pointe retrieved from EudraVigilance. Belgium confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### **Discussion**

The PRAC discussed the results of the study by *Poluzzi E. et al.* as well as the additional cases reported in EudraVigilance. The PRAC noted that the publication was based on an analysis of the FDA Adverse Event Reporting System in which a large proportion of reports are consumer cases. Having considered the available evidence, the PRAC has agreed that an additional analysis of the EudraVigilance data should be performed before deciding whether to support the proposed cumulative review for loratadine or any decision to extend such a review to desloratadine, diphenhydramine, fexofenadine and/or cetirizine.

The PRAC appointed Veerle Verlinden as Rapporteur for the signal.

#### **Summary of recommendation(s)**

- The PRAC agreed that an additional analysis of the EudraVigilance data before deciding whether to support the proposed cumulative review for loratadine or any decision to extend such a review to desloratadine, diphenhydramine, fexofenadine and/or cetirizine should be performed by EMA. The signal is planned for further discussion at the March 2016 PRAC meeting.

---

<sup>2</sup> Poluzzi E, Raschi E, Godman B, Koci A, Moretti U, Kalaba M, Wettermark B, Sturkenboom M, De Ponti F. Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. PLoS One. 2015 Mar 18;10(3):e0119551

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

#### 4.1.7. Natalizumab – TYSABRI (CAP)

---

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of necrotising retinitis  
EPITT 18605 – New signal  
Lead Member State: DE

##### **Background**

Natalizumab is a recombinant humanised anti- $\alpha$ 4-integrin antibody indicated for the treatment of single disease modifying therapy in highly active relapsing remitting multiple sclerosis under certain conditions.

The post-marketing exposure for Tysabri, a centrally authorised medicine containing natalizumab, is estimated to have been more than 440,054 patient-years worldwide, in the period from first authorisation in 2006 until July 2015.

During routine signal detection activities, a signal of necrotising retinitis was identified by the EMA, based on 5 supportive cases retrieved from EudraVigilance (4 cases) and from the literature (1 case). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

##### **Discussion**

The PRAC discussed the available evidence from case reports in EudraVigilance and from published case reports in the literature. Having considered the seriousness of necrotising retinitis, and the available evidence, the PRAC recommended that the MAH for Tysabri should submit a cumulative review of all relevant data from all sources related to necrotising retinopathy, necrotising herpetic retinopathy and necrotising retinitis associated with Herpes viruses (e.g. varicella zoster virus, cytomegalovirus, herpes simplex virus), other pathogens and cases where no pathogens have been identified.

##### **Summary of recommendation(s)**

- The MAH for Tysabri (natalizumab) should submit to the EMA, within 60 days, a cumulative review of all relevant data from all sources related to necrotising retinopathy, necrotising herpetic retinopathy and necrotising retinitis associated with Herpes viruses, other pathogens and cases where no pathogens have been identified. This review should include information on the clinical course, the management of the disease and the clinical outcome. The MAH may also present cases of herpes infections resulting in other ophthalmologic complications. Special attention should be paid to immune reconstitution inflammatory syndrome in the clinical course of the eye infection. The MAH should also propose any potential amendment to the product information and/or the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

### 4.2.1. Quinine (NAP)

---

Applicant: various

PRAC Rapporteur: Almath Spooner

Scope: Signal of an increased mortality risk in heart failure patients with/without concomitant use of beta-blockers

EPITT 18529 – New signal

Lead Member State: IE

#### Background

Quinine is a cinchona alkaloid indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria and chloroquine-resistant malaria and for nocturnal leg cramps.

Following the publication by *Gjesing et al.*<sup>3</sup>, a signal of an increased mortality risk in heart failure patients with/without concomitant use of beta-blockers was identified by Denmark. Ireland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

The PRAC discussed the results of the published study by *Gjesing et al.* and noted that the study has some methodological limitations. However, in the context of the known safety profile of quinine and quinidine and the characteristics of the population likely to be treated (of which quinine is the chemical right R-isomer), the PRAC considered that the innovator MAHs (Sanofi and Takeda Pharm A/S) should carefully review the study and provide a critical analysis of the issue in the context of other published scientific literature, epidemiological studies, post-marketing data and clinical trial data.

#### Summary of recommendation(s)

- The innovator MAHs (Sanofi and Takeda Pharma A/S) should submit to the EMA, within 60 days, a critical analysis of the issue in the context of other published scientific literature, epidemiological studies, post-marketing data and clinical trial data.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.2.2. Warfarin (NAP)

---

Applicant: various

PRAC Rapporteur: Torbjorn Callreus

Scope: Signal of calciphylaxis

EPITT 18545 – New signal

Lead Member State: DK

#### Background

---

<sup>3</sup> Gjesing A., Gislason G.H., Christensen S.B. and al. Use of quinine and mortality-risk in patients with heart failure—a Danish nationwide observational study; *Pharmacoepidemiology and Drug Safety*; Volume 24, Issue 3, pages 310–318, March 2015

Warfarin is an oral anticoagulant used for short and long term prevention of thromboembolic disorders, including treatment and prevention of deep venous thrombosis and pulmonary embolism, secondary prevention of myocardial infarction and prevention of thromboembolic complications (stroke or systemic embolism) after myocardial infarction, and for prevention of thromboembolic complications in patients with atrial fibrillation, cardiac valvular disease or prosthetic heart valves.

The worldwide exposure for medicines containing warfarin is estimated to have been very large, due to the fact that the medicine has been extensively prescribed since its first authorisation in the mid-1950s.

A signal of calciphylaxis was raised by Sweden, following a request from the MAH for Warfarin Orion to update the product information to add calciphylaxis as a new undesirable effect as part of a renewal procedure and based on 23 supportive cases (7 raised by the MAH and 16 from the literature). Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the available evidence from spontaneous cases, as well as from the literature. Taking into account that calciphylaxis is a rare but serious event, that a causal relationship between warfarin and calciphylaxis cannot be ruled out despite confounding factors in the described cases, and that protein C and/or S deficiency is a risk factor for calciphylaxis, the PRAC agreed that the originator MAHs should provide a cumulative review of all cases of calciphylaxis associated with warfarin.

The PRAC appointed Torbjorn Callreus as Rapporteur for the signal.

### **Summary of recommendation(s)**

- The originator/market lead MAHs (Takeda and Bristol-Myers Squibb) should submit to the EMA, within 60 days, a cumulative review of all cases of calciphylaxis and other related terms in association with warfarin. The MAHs should include preclinical and in vitro data, as well as relevant literature, and discuss the possible mechanism of action. The MAHs should also discuss the need for any potential amendment to the product information and/or the risk management plan and, within this discussion, make a proposal as applicable. Based on the conclusion of the cumulative review, the MAHs may propose the appropriate frequency for calciphylaxis and discuss the inclusion of a warning for susceptible individuals at higher risk of developing the adverse drug reaction, such as patients with renal impairment, diabetes, protein C and S deficiency and other relevant patient groups.
- 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. Methotrexate (NAP)**

---

Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of progressive multifocal leukoencephalopathy (PML) and JC<sup>4</sup> virus infection  
EPITT 18473 – Follow-up to September 2015

### **Background**

For background information, see [PRAC minutes September 2015](#). The MAHs replied to the request for information on the signal of progressive multifocal leukoencephalopathy (PML) and JC virus infection and the responses were assessed by the Rapporteur.

### **Discussion**

The PRAC discussed the MAHs' responses. Based on the responses provided by the consulted MAHs, and taking into consideration the long marketing authorisation experience with methotrexate, the PRAC concluded that the data currently available do not present sufficient unconfounded evidence to confirm an increased risk of PML associated with methotrexate. The risk of progressive multifocal leukoencephalopathy should however remain under close monitoring as an important safety concern by the MAHs of methotrexate-containing medicinal products.

### **Summary of recommendation(s)**

- The MAHs of methotrexate-containing medicinal products should continue to closely monitor case reports of progressive multifocal leukoencephalopathy as part of routine safety surveillance.

#### **4.3.2. Oxybutynin – KENTERA (CAP) - EMEA/H/C/000532/SDA/021**

---

Applicant: Nicobrand Limited

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of psychiatric disorders  
EPITT 18342 – Follow-up to November 2015

### **Background**

For background information, see [PRAC minutes June 2015](#) and [PRAC minutes November 2015](#). The MAH for Kentera replied to the request for information on the signal of psychiatric disorders and the responses were assessed by the Rapporteur. Also following the request of the PRAC, the Paediatric Committee (PDCO) provided input on the use of oxybutynin in the paediatric population.

### **Discussion**

The PRAC discussed the MAHs' responses, as well as the feedback from the PDCO on the use of oxybutynin in the paediatric population. The PDCO supported the inclusion of a safety warning regarding the adverse effects in the paediatric population in the product information as proposed by the PRAC, together with wording as appropriate clarifying that transdermal formulations of oxybutynin are not indicated for use in the paediatric population.

Having considered the responses submitted from the MAH of Kentera, the evidence from clinical trials and the plausible biological mechanism, as well as the information received

---

<sup>4</sup> John Cunningham virus (JCV)



from the PDCO, the PRAC agreed that the product information for transdermal oxybutynin-containing products (patch, gel in sachet, metering pump) should be updated regarding the risk of psychiatric and central nervous system (CNS) adverse effects.

With regards to the association between transdermal oxybutynin and depression, the PRAC agreed that there is not enough evidence to conclude on a possible causal relationship and therefore this event should continue to be closely monitored as part of routine safety surveillance.

#### **Summary of recommendation(s)**

- The MAHs of transdermal (patch, gel in sachet, metering pump) oxybutynin-containing medicinal products should submit to the relevant EU national competent authorities (NCAs), within 60 days, a variation to include information on the special populations 'elderly' and 'paediatric population' in the dosing section, to include a new warning on psychiatric and central nervous system adverse effects, and to add as new undesirable effects psychiatric disorders and central nervous system disorders.
- The MAHs of transdermal oxybutynin-containing medicinal products (patch, gel in sachet, metering pump) should continue to closely monitor case reports of depression as part of routine safety surveillance.

For the full PRAC recommendations, see [EMA/PRAC/1275/2016](https://www.ema.europa.eu/en/press-room/2016/04/wg-prac-recommendations-1275-2016) published on the EMA website.

#### **4.3.3. Paracetamol (NAP), phenylephrine (NAP)<sup>5</sup>**

---

Applicant: various

PRAC Rapporteur: Veerle Verlinden

Scope: Signal of pharmacokinetic drug interaction increased bioavailability of phenylephrine when co-administered with paracetamol  
EPITT 18474 – Follow-up to September 2015

#### **Background**

For background information, see [PRAC minutes September 2015](#). The MAHs replied to the request for information on the signal of increased bioavailability of phenylephrine when co-administered with paracetamol via a pharmacokinetic drug interaction, and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC discussed the MAHs' responses. Taking into account these responses and the evidence from the literature, the PRAC agreed that the existing information in the product information is currently sufficient and therefore does not require any change at this point. However the potential adverse effects relating to the pharmacokinetic interaction between paracetamol and phenylephrine should continue to be closely monitored as part of routine safety surveillance.

#### **Summary of recommendation(s)**

---

<sup>5</sup> And combination paracetamol/phenylephrine (NAP)

- The MAHs of paracetamol and phenylephrine-containing medicinal products should continue to monitor the pharmacokinetic interaction between paracetamol and phenylephrine as part of routine safety surveillance.

#### 4.3.4. Peginterferon alfa-2a – PEGASYS (CAP) – EMEA/H/C/000395/SDA/055

---

Applicant: Roche Registration Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Signal of Guillain-Barré syndrome (GBS)  
EPITT 18402 – Follow-up to September 2015

##### **Background**

For background information, see [PRAC minutes September 2015](#). The MAH replied to the request for information on the signal of Guillain-Barré syndrome (GBS) and the responses were assessed by the Rapporteur.

##### **Discussion**

The PRAC discussed the MAH's responses. Having considered the data from spontaneous reports, epidemiological data, non-clinical studies, clinical trials and the literature provided by the MAH for Pegasys (Peginterferon alfa-2a) in its cumulative review, the PRAC concluded that there is insufficient evidence of an association between peginterferon alfa-2a and Guillain-Barré syndrome.

##### **Summary of recommendation(s)**

- No regulatory action was considered necessary based on the evaluation of this signal.

#### 4.3.5. Recombinant factor VIII: antihemophilic factor (recombinant) (NAP) moroctocog alfa – REFACTO AF (CAP) octocog alfa – ADVATE (CAP), HELIXATE NEXGEN (CAP), KOGENATE (CAP)

---

Applicant: Baxter AG (Advate, Recombinate), Bayer Pharma AG (Kogenate, Helixate NexGen), Pfizer Limited (ReFacto AF), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of inhibitor development in previously untreated patients (PUP)  
EPITT 18134 – Follow-up to May 2015

##### **Background**

For background information, see [PRAC minutes November 2014](#), [PRAC minutes December 2014](#), [PRAC minutes January 2015](#), [PRAC minutes March 2015](#) and [PRAC minutes May 2015](#).

##### **Discussion**

The PRAC Rapporteur presented a summary of the findings of the meta-analysis performed according to a previously agreed action plan. The PRAC recommended that the PRAC co-Rapporteur assesses the results of the analysis within a 60-day timetable, leading to a final PRAC recommendation.

### Summary of recommendation(s)

- The PRAC co-Rapporteur for Kogenate (Ulla Wändel Liminga) should assess the results of the meta-analysis, within 60 days, leading to a final PRAC recommendation.

#### 4.3.6. Saxagliptin – ONGLYZA (CAP)- EMEA/H/C/001039/SDA/0039; saxagliptin, metformin – KOMBOGLYZE (CAP) - EMEA/H/C/002059/SDA/016

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Signal of acute kidney injury  
EPITT 18379 – Follow-up to July 2015

### Background

For background information, see [PRAC minutes July 2015](#). The MAH replied to the request for information on the signal of acute kidney injury and the responses were assessed by the Rapporteur.

### Discussion

The PRAC discussed the MAH's responses. Having considered the available evidence from EudraVigilance, the literature and the data submitted by the MAH, the PRAC noted that a causal association between saxagliptin and acute renal failure cannot completely be excluded; however the weight of the evidence that is currently available is considered insufficient to justify an update to the product information or the RMP. The PRAC therefore agreed to close the signal procedure and to await the results of the observational study CV181157 ST (a category 3 as per the RMP), due in May 2016, in which the risk of hospitalisation for acute kidney injury is being investigated, and will re-assess all available evidence together. As part of the submission of the final clinical study report (CSR) for study CV181157 ST, the MAH should also provide a thorough review of the literature including abstracts and references.

### Summary of recommendation(s)

- No regulatory action was considered necessary based on the evaluation of this signal at this point in time but the results of observational study CV181157 ST are awaited.
- The MAH for Onglyza (saxagliptin) and Komboglyze (saxagliptin, metformin) should provide a thorough review of the literature including abstracts and references when submitting to EMA the final results of study CV181157 ST.

#### 4.3.7. Thioctic acid (NAP)

---

Applicant: Biologische Heilmittel Heel GmbH

PRAC Rapporteur: Marina Dimov Di Giusti

Scope: Signal of insulin autoimmune syndrome (IAS)  
EPITT 18406 – Follow-up to September 2015

### Background

For background information, see [PRAC minutes September 2015](#). Following the PRAC recommendation adopted in September 2015, Biologische Heilmittel Heel GmbH, a MAH of homeopathic products containing thioctic acid, requested clarification as to whether the PRAC recommendation (submission of variations to update the product information) for the signal of IAS, adopted in September 2015, should be applicable for homeopathic products.

### **Discussion**

The PRAC discussed Biologische Heilmittel Heel GmbH's request considering that the PRAC recommendation adopted in September 2015 was based on case reports for allopathic products and food supplements with daily doses ranging from 200 to 600 mg of thioctic acid. The dose of thioctic acid was not expected to play a major role in the development of IAS, taking into account the immune component of the disease. Also, the PRAC acknowledged that the mechanism of development of IAS is not clearly understood. Having considered the additional data submitted by Biologische Heilmittel Heel GmbH with regards to homeopathic products containing thioctic acid, the PRAC agreed that no further action should be taken at EU level for homeopathic medicinal products containing thioctic acid.

### **Summary of recommendation(s)**

- No further action should be taken at the EU level by the MAHs of homeopathic medicinal products containing thioctic acid.
- The National Competent Authorities in the Member States may consider actions at national level as appropriate.

## **5. Risk management plans (RMPs)**

### **5.1. Medicines in the pre-authorisation phase**

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

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

See also Annex I. 14.1.

#### **5.1.1. Allogeneic T cells genetically modified to express suicide gene - EMEA/H/C/002801, Orphan, ATMP<sup>6</sup>**

---

Applicant: MolMed SpA

Scope: Treatment in haploidentical haematopoietic stem cell transplantation

#### **5.1.2. Daratumumab - EMEA/H/C/004077, Orphan**

---

Applicant: Janssen-Cilag International N.V.

---

<sup>6</sup> Advanced-therapy medicinal product

Scope (accelerated assessment): Treatment of patients with relapsed and refractory multiple myeloma

### **5.1.3. Eftrenonacog alfa - EMEA/H/C/004142, Orphan**

---

Applicant: Biogen Idec Ltd

Scope: Treatment and prophylaxis of bleeding in patients with haemophilia B

### **5.1.4. Pandemic influenza vaccine H5N1 (live attenuated, nasal) - EMEA/H/C/003963**

---

Scope: Prophylaxis of influenza

### **5.1.5. Zonisamide - EMEA/H/C/004127**

---

Scope: Treatment of epilepsy

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

See Annex I. 14.2.

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

See also Annex I. 14.3.

### **5.3.1. Lenalidomide – REVLIMID (CAP) - EMEA/H/C/000717/II/0079**

---

Applicant: Celgene Europe Limited

PRAC Rapporteur: Corinne Fechant

Scope: Extension of indication to add the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated accordingly. The RMP (version 25.0) is updated accordingly

#### **Background**

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

The CHMP is evaluating an extension of the therapeutic indication for Revlimid, a centrally authorised product containing lenalidomide, to include the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (RRMCL). 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 March 2015](#), [PRAC minutes July 2015](#) and [PRAC minutes October 2015](#).

#### **Summary of advice**

- The RMP version 28.0 for Revlimid (lenalidomide) in the context of the variation under evaluation by the CHMP could be acceptable provided that satisfactory responses are received to a request for supplementary information.
- The PRAC considered that the proposed PASS on RRMCL patients should be included in the RMP as a category 3 study to further investigate and characterise the association of lenalidomide and tumour flare reaction (TFR)/high tumour burden. In addition, the MAH should submit to EMA, within 120 days after the CHMP opinion, a full protocol based on existing data collection systems. The PRAC underlined the need to duly take into consideration the TFR/high tumour burden questionnaire to qualify as well as possible the data that will be collected and analysed in the PASS. In addition, the PRAC considered that arterial thromboembolism (ATE), venous thromboembolism (VTE) and second primary malignancy (SPM) should be removed from the proposed PASS protocol objectives. Instead, the MAH should implement a specific targeted follow-up questionnaire to study the relationship between lenalidomide and TFR/high tumour burden, ATE, VTE and SPM and update the RMP accordingly.

## 6. Periodic safety update reports (PSURs)

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

See also Annex I. 15.1.

#### 6.1.1. Azacitidine – VIDAZA (CAP) - PSUSA/00274/201505 (with RMP)

Applicant: Celgene Europe Limited

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### Background

Azacitidine is a pyrimidine analogue indicated for the treatment of adult patients with intermediate-2 and high-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML) who are not eligible for haematopoietic stem cell transplantation (HSCT), under certain conditions.

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

#### Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vidaza (azacitidine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on tumour lysis syndrome and to include pyoderma gangrenosum as a new undesirable

effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>7</sup>.

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.

### 6.1.2. Cabazitaxel – JEVTANA (CAP) - PSUSA/00476/201506

---

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

#### **Background**

Cabazitaxel is an antineoplastic agent indicated in combination with prednisone or prednisolone for the treatment of adult patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Jevtana (cabazitaxel) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on interstitial pneumonia/pneumonitis, interstitial lung disease and the need for close monitoring in case of new or worsening pulmonary symptoms, and on bone marrow suppression. In addition, the product information should be updated in the undesirable effects section of the SmPC to include that cases of interstitial pneumonia/pneumonitis and interstitial lung disease (ILD) have been reported. Therefore the current terms of the marketing authorisation(s) should be varied<sup>8</sup>.
- In the next PSUR, the MAH should provide a cumulative review of all spinal cord compression events and of all hepatic failure events. The MAH should review the analysis of cardiac arrhythmia cases provided within the present PSUR and should provide the same detailed analysis for cardiac arrhythmia cases reported during the period covered by the next PSUR. The MAH should provide an accurate review of respiratory disorders cases and a clear review of reported medication errors. The MAH should discuss an update of the product information regarding determination of frequency of ILD and related events, and should provide supportive data. Finally, the MAH should provide a cumulative analysis of all radiation cystitis cases and also all radiation recall phenomena cases received, and discuss a potential update of the product information.

---

<sup>7</sup> 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

<sup>8</sup> 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

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. Gefitinib – IRESSA (CAP) - PSUSA/01518/201507

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Iressa (gefitinib) 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 6 months, a type II variation discussing the need to update the product information, based on all available data, once the final clinical study report of a failed study evaluating the efficacy and safety of continuing gefitinib, in addition to chemotherapy, versus chemotherapy alone in patients who have EGF mutation positive locally advanced or metastatic NSCLC and have progressed on first line gefitinib becomes available.
- The MAH should submit to the EMA, within 60 days, a literature review on the mechanisms of resistance to gefitinib by transformation of non-small cell lung cancer and lung adenocarcinoma to small cell carcinoma. The MAH should discuss the need to update the product information, based on a critical assessment of the information available. In particular, the need to add a paragraph concerning 'mechanisms of resistance, including secondary resistance-related mutations, activation of alternative signalling pathways, phenotypic switch' should be discussed in a post-authorisation measure (LEG) or a type II variation, as appropriate.
- The MAH should critically appraise a safety meta-analysis reporting a higher frequency of cases of gefitinib-related hepatotoxicity of grade  $\geq 3$  in Asians compared to non-Asians<sup>9</sup>. Based on this appraisal, the MAH should discuss, in a post-authorisation measure (LEG) or type II variation, as appropriate, the need to include information on potential differences between Asian and non-Asian populations in addition to the information already included in the product information regarding hepatotoxicity.

---

<sup>9</sup> Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. *Lung Cancer*. 2015 Apr; 88(1):74-9



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.

#### 6.1.4. Mirabegron – BETMIGA (CAP) - PSUSA/10031/201506 (with RMP)

---

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

##### **Background**

Mirabegron is a beta 3-adrenoceptor agonist indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

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

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Betmiga (mirabegron) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include as new undesirable effects dizziness, constipation, headache and diarrhoea with a common frequency and hypertensive crisis with a very rare frequency. In addition, the package leaflet is updated accordingly, together with information regarding the possible relationship between severe headaches and hypertensive crisis. Therefore the current terms of the marketing authorisation(s) should be varied<sup>10</sup>.
- In the next PSUR, the MAH should submit a cumulative review of cases of haematuria, hypertension and tremor. Based on the output of these reviews, a proposal for changes to the product information should be provided. The MAH should also provide a cumulative review of atrial fibrillation cases that reported other cardiac events, particularly cardiac ischaemia and cardiac failure. The MAH should explore the cases with pre-existing atrial-fibrillation. If necessary, a warning about atrial fibrillation in the product information should be proposed by the MAH. Finally the MAH should discuss the article by *Alexandre EC et al.*<sup>11</sup> and its impact on the safety profile of mirabegron  $\beta$ 3 -adrenoceptor activation and  $\alpha$ 1-adrenoceptor blockade.
- The MAH should include 'cardiac failure, particularly in patients with pre-existing cardiovascular diseases or cardiovascular risk factors' as an important potential risk instead of as missing information within the next update of the RMP.

---

<sup>10</sup> 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

<sup>11</sup> Alexandre EC, Kiguti LR, Calmasini FB, Silva FH, da Silva KP, Ferreira R, Ribeiro CA, Mónica FZ, Pupo AS, Antunes E. Mirabegron relaxes urethral smooth muscle by a dual mechanism involving  $\beta$ 3 -adrenoceptor activation and  $\alpha$ 1 -adrenoceptor blockade; Br J Pharmacol. 2016 Feb;173(3):415-28. doi: 10.1111/bph.13367. Epub 2016 Jan 15

- The MAH should also update the product information regarding interaction with other medicinal products and other forms of interaction in accordance with relevant guidelines to provide clearer information on interactions at the next relevant regulatory opportunity.

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

#### **6.1.5. Ponatinib – ICLUSIG (CAP) - PSUSA/10128/201506 (with RMP)**

---

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ponatinib is a protein kinase inhibitor indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) and for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) under certain conditions.

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

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Iclusig (ponatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypothyroidism as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>12</sup>.
- In the next PSUR, the MAH should provide detailed reviews of cases of diabetes, renal failure, seizures, pulmonary oedema and eye haemorrhage including a discussion of whether any action is required in relation to these cases. The MAH should continue to provide in future PSURs information on the incidence rates of vascular occlusive events from further follow up of clinical trials.

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

#### **6.1.6. Sofosbuvir – SOVALDI (CAP) - PSUSA/10134/201506 (with RMP)**

---

Applicant: Gilead Sciences International Ltd

<sup>12</sup> 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

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

### **Background**

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B RNA<sup>13</sup>-dependent RNA polymerase indicated in combination for the treatment of chronic hepatitis C (CHC) in adults.

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

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sovaldi (sofosbuvir) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should update its cumulative review of bradycardia and heart block events, to include in particular a review of cases without concomitant amiodarone use and cases reported in patients with existing cardiac rhythm disorders. As an outcome, the MAH should consider the need for any update of the product information regarding the current wording on the risk of bradycardia with sofosbuvir (SOF) + daclatasvir (DCV) and amiodarone, as well as the adequacy and accuracy of the current undesirable effects section. Moreover, the MAH should conduct a detailed review of cases of cardiac failure/insufficiency, including reports from post-marketing, clinical trial data and the literature. Any relevant data on the SOF-containing product Harvoni should also be presented. The MAH should also provide an updated review of the worsening of hepatic disease. Furthermore, the MAH should provide an updated review of cases of pulmonary arterial hypertension (PAH), together with a thorough discussion on potential plausibility of PAH being associated with sofosbuvir use. Finally, within the review of the missing information 'safety in patients with severe renal failure and end stage renal disease (ESRD)', the MAH should provide a cumulative review of renal events, including a discussion of any interim results from study GS-US-334-0154 and other relevant studies which may be available, and a literature review.

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

#### **6.1.7. Trametinib – MEKINIST (CAP) - PSUSA/10262/201505**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

### **Background**

---

<sup>13</sup> Non-structural protein 5B ribonucleic acid

Trametinib is a protein kinase inhibitor indicated in monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Mekinist (trametinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on colitis and gastrointestinal perforation and to include as new undesirable effects colitis and intestinal perforation with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>14</sup>.
- In the next PSUR, the MAH should provide CIOMS<sup>15</sup> forms of new cases of adverse reactions of myocarditis and related terms including granulomatous myocarditis. The MAH should also provide a safety topic review on bradycardia.
- In the next update of the RMP the MAH should include colitis and gastrointestinal perforation as part of the new important identified risk 'gastrointestinal disorders' which can also include diarrhoea (currently listed as an important identified risk). This should apply to trametinib monotherapy and trametinib in combination with dabrafenib. In addition, in light of accumulating data, the MAH should review the existing safety concerns within the safety specification to determine whether any of these are suitable for removal.

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

#### **6.1.8. Umeclidinium bromide, vilanterol – ANORO (CAP), LAVENTAIR (CAP) - PSUSA/10264/201506**

---

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

#### **Background**

Umeclidinium is an inhaled long-acting muscarinic receptor antagonist and in combination with vilanterol, a long-acting beta<sub>2</sub>-adrenergic agonist (LAMA/LABA), is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

---

<sup>14</sup> 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

<sup>15</sup> Council for International Organizations of Medical Sciences

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

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Anoro and Laventair (umeclidinium bromide, vilanterol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include glaucoma as a new undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.
- In the next PSUR, the MAH should closely monitor cases of dementia and provide a cumulative review of cases. The MAH should also provide the reporting rate of medication errors and of events with fatal outcome. The MAH should provide a cumulative review of bladder outflow obstruction and urinary retention cases taking into account all the information from clinical trials, spontaneous reports, and published literature, with a focus on whether there is sufficient evidence to update the product information. Finally the MAH should further investigate the type and the severity of glaucoma. Moreover the MAH should discuss separately cases of glaucoma and cases reported under other preferred terms clinically related to glaucoma, and which population is at risk.
- The MAH should be requested to include glaucoma as a new important identified risk in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP.

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

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

See also Annex I. 15.2.

### **6.2.1. Topotecan – Hycamtin (CAP), Potactasol (CAP), Topotecan Actavis (CAP), Topotecan Hospira (CAP), Topotecan Teva (CAP), NAP - PSUSA/02997/201505**

---

Applicant: Actavis Group PTC ehf, Hospira UK Limited, Novartis Europharm Ltd, Teva B.V., various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **Background**

---

<sup>16</sup> 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

Topotecan is a topoisomerase-I inhibitor indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy and for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. In combination with cisplatin, topotecan is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hycamtin, Potactasol, Topotecan Actavis, Topotecan Hospira and Topotecan Teva, centrally authorised medicines containing topotecan, and nationally authorised medicines containing topotecan, and issued a recommendation on their marketing authorisations.

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of topotecan-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to remove chemotherapy-induced diarrhoea, bone marrow suppression, neutropenic colitis, gastrointestinal symptoms, infection, interstitial lung disease and overdose from the list of safety concerns.

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

### **6.3. PSUR procedures including nationally authorised products (NAPs) only**

See also Annex I. 15.3.

#### **6.3.1. Apomorphine (NAP) - PSUSA/0000227/201505**

---

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### **Background**

Apomorphine is a non-selective dopamine agonist which activates both D1-like and D2-like receptors indicated for the treatment of motor fluctuations ('on/off' phenomena) in patients with Parkinson's disease (PD) which is not sufficiently controlled by oral anti-Parkinson medication. Apomorphine is also indicated as a pro-emetic for use after acute poisoning, for which fast-onset removal of the poison is necessary and lethal outcome or severe complications can be expected.

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

The PRAC discussed the conclusions reached by the Scientific Advisory Group (SAG) on Neurology convened via written procedure. The PRAC noted that the SAG confirmed that the risk minimisation measures resulting from the referral<sup>17</sup> procedure on domperidone ([EMA/152501/2014](#)) had been reflected in EU guidance on use of apomorphine in Parkinson's disease.

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of apomorphine-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated in the 'Posology and method of administration' section to amend the information on concomitant use of domperidone with apomorphine regarding the domperidone dose and the need for careful assessment of risk factors of QT prolongation. In addition the product information should be updated to include further advice on the use of domperidone before and during apomorphine treatment in the 'Special warnings and precautions for use' section, including electrocardiograms (ECGs) before and at appropriate intervals during treatment. Finally the product information should be updated to include as new undesirable effects hallucination with a very common frequency, syncope with an unknown frequency and to remove the wording regarding neuropsychiatric disturbances from the undesirable effects section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- The new recommendations should be communicated through appropriate channels to inform the medical community. The need for further communication at national level could be considered by the relevant competent authorities.
- In the next PSUR, to provide the available evidence on the safety and benefits on the combined use of apomorphine and domperidone, the MAHs of apomorphine-containing medicinal products with the Parkinson's disease indication should provide a literature review and a cumulative review of their safety database regarding the risk of QT prolongation. The MAHs should also cumulatively evaluate the issues 'impulse control disorders', 'punding' and 'dopamine agonist withdrawal syndrome' and discuss whether any update of the product information may be required. In the latter analysis cases of abuse, dependence and similar disorders should also be considered by the MAHs as these are closely related. Finally the MAHs should provide cumulative evidence from literature and individual case safety reports on the following topics: psychotic disorders, depression, anxiety and aggression/agitation.

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

---

<sup>17</sup> Article 31 of Directive 2001/83/EC

<sup>18</sup> Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

6-monthly to three-yearly and the list of Union reference dates (EURD list) will be updated accordingly.

### 6.3.2. Bismuth subcitrate potassium, metronidazole, tetracycline (NAP) - PSUSA/00010199/201505

---

Applicant: various

PRAC Lead: Viola Macolić Šarinić

Scope: Evaluation of a PSUSA procedure

#### **Background**

Bismuth subcitrate potassium is a salt of bismuth, potassium and citrate. Bismuth is a chemical element and a pentavalent post-transition metal, and chemically resembles arsenic and antimony. Metronidazole is an antibiotic and antiprotozoal medication. Tetracycline is a broad-spectrum antibiotic of the polyketide class. Bismuth subcitrate potassium, metronidazole, tetracycline is a combination indicated for the eradication of helicobacter pylori and prevention of relapse of peptic ulcers in patients with active or a history of helicobacter pylori associated ulcers in combination with omeprazole (quadruple therapy).

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of medicinal products containing bismuth subcitrate potassium, metronidazole, tetracycline in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include encephalopathy as a new undesirable effect with a very rare frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>19</sup>.
- In the next PSUR, the MAHs should routinely monitor the following topics and provide the data routinely in future PSURs: reactions with fatal outcome, drug use during pregnancy and lactation, overdose, lack of efficacy, off-label use, and misuse. The MAHs should also present an overview of cases reporting treatment failure, multiple-drug resistance and preferred terms related to disease (re)-occurrence. Finally the MAHs should present a short overview of the important potential risk 'use in special populations' and present and/or cross-reference the cases received in the monitoring period.

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.

---

<sup>19</sup> 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



### 6.3.3. Gadobenic acid (NAP) - PSUSA/00001500/201504

---

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadobenic acid is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI). Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing gadobenic acid, and issued a recommendation on their marketing authorisations.

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadobenic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadobenic acid does not cross the intact blood-brain barrier in the 'Pharmacokinetic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.
- The MAHs which have an RMP in place should be requested in the next RMP update to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissue' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'. Finally, the MAHs should also include as category 3 studies in the Pharmacovigilance plan the ongoing MRI study and the two non-clinical studies FRCG-03-15 and BIO 2/15.

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. Gadobutrol (NAP) - PSUSA/00001502/201504

---

Applicant: various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadobutrol is a paramagnetic macrocyclic gadolinium-based contrast agent for magnetic resonance imaging and is indicated in adults and children of all ages for contrast enhancement in cranial and spinal MRI, contrast-enhanced MRI of the whole body and contrast enhancement in magnetic resonance angiography (MRA).

---

<sup>20</sup> Update of SmPC section 5.2. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadobutrol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadobenate ion does not cross the intact blood-brain barrier in the 'Pharmacodynamic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- The MAHs which have an RMP in place should be requested in the next RMP update to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

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. Gadodiamide (NAP) - PSUSA/00001503/201504**

---

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadodiamide is a gadolinium-based magnetic resonance imaging (MRI) contrast agent, indicated for intravenous use in adults and children for MRI of the central nervous system and whole body, and for angiography.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadodiamide-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include skin plaque as new undesirable effect with a not known frequency and to remove the statement that gadodiamide does not cross the intact blood-brain barrier in the 'Pharmacokinetic

---

<sup>21</sup> Update of SmPC section 5.1. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.

- In the next PSUR, the MAHs should make efforts to follow up the effectiveness of the risk minimisation measures for the safety concerns in the RMP and should continue to monitor the use and to evaluate the risk/benefit in paediatric patients
- The MAHs of gadolinium products which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

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

### 6.3.6. Gadopentetic acid (NAP) - PSUSA/00001504/201504

---

Applicant: various

PRAC Lead: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadopentetic acid is a gadolinium-based paramagnetic contrast agent for magnetic resonance imaging (MRI), indicated for cranial and spinal MRI, whole body MRI, demonstration and demarcation of the digestive tract from adjacent normal and pathological tissue structures in MRI and contrast enhancement in magnetic resonance arthrography.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadopentetic acid-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadopentetic acid does not cross the intact blood-brain barrier in the 'Pharmacokinetic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAHs should discuss two literature articles documenting gadolinium associated skin plaques with sclerotic bodies and focal calcification in three

---

<sup>22</sup> Update of SmPC sections 4.8 and 5.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>23</sup> Update of SmPC section 5.2. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

patients without nephrogenic systemic fibrosis following multiple gadolinium contrast agent administrations from *Gethings et al.*<sup>24</sup> and *Bhawan et al.*<sup>25</sup>

- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

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.

### 6.3.7. Gadoteric acid (intravenous and intravascular formulations) (NAP) - PSUSA/00001506/201504

---

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadoteric acid in intravenous and intravascular formulation is a solution for injection, and is a paramagnetic contrast agent for magnetic resonance imaging (MRI). It is for diagnostic use only and is authorised for use for intensification of the contrast in MRI for a better visualisation/delineation of lesions of the brain, spine, and surrounding tissues in adults and paediatrics (0-18 years), lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system in adults and paediatrics (0-18 years) and lesions or stenoses of the non-coronary arteries (magnetic resonance angiography).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing gadoteric acid (intravenous and intravascular formulations), and issued a recommendation on their marketing authorisations.

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadoteric acid- containing medicinal products (intravenous and intravascular formulations) in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadoteric acid (intravenous and intravascular formulations) does not cross the intact blood-brain barrier in the 'Pharmacokinetic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.

---

<sup>24</sup> Gethings RM, Reddy R, Sant Cruz D, Brodell RT. Gadolinium-associated plaques: a new, distinctive clinical entity. *JAMA Dermatol* 2015; 151(3): 316-9

<sup>25</sup> Bhawan J, Perez-Chua TA, Goldberg L. Sclerotic bodies beyond nephrogenic systemic fibrosis. *J Cutan Pathol* 2013; 40(9): 812-7

<sup>26</sup> Update of SmPC section 5.2. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

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.

### 6.3.8. Gadoteridol (NAP) - PSUSA/00001507/201504

---

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadoteridol is gadolinium-based magnetic resonance imaging (MRI) contrast agent indicated for use in MRI to produce contrast enhancement in the brain, spine and surrounding tissues, resulting in improved visualisation (compared to unenhanced MRI) of lesions with abnormal vascularity or those thought to cause a disruption of the blood-brain barrier. Gadoteridol is also indicated for whole body MRI, including the head, neck, liver, breast, musculoskeletal system, and soft tissue pathologies.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadoteridol-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadoteridol does not cross the intact blood-brain barrier in the 'Pharmacodynamic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>27</sup>.
- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

---

<sup>27</sup> Update of SmPC section 5.1. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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.

### 6.3.9. Gadoxetic acid disodium (NAP) - PSUSA/00001509/201504

---

Applicant: various

PRAC Lead: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### **Background**

Gadoxetic acid disodium is a paramagnetic contrast agent for diagnostic use indicated for intravenous (IV) administration for T1-weighted magnetic resonance imaging (MRI) of the liver.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of gadoxetic acid disodium -containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to remove the statement that gadoxetic acid disodium does not cross the intact blood-brain barrier in the 'Pharmacokinetic properties' section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.
- In the next PSUR, the MAHs should make efforts to follow up the effectiveness of the risk minimisation measures for the safety concerns in the RMP.
- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of Gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

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.

### 6.3.10. Iodine (<sup>131</sup>I) iobenguane (NAP) - PSUSA/00001764/201505

---

Applicant: various

---

<sup>28</sup> Update of SmPC section 5.2. 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**

Iodine ( $^{131}\text{I}$ ) iobenguane is a radioiodinated aralkylguanidine. It is a diagnostic agent indicated for calculation of a therapeutic ( $^{131}\text{I}$ ) iobenguane dose from a prior tracer-dose. It is indicated for radiation therapy of tumour-tissue that is capable of retaining iobenguane.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines containing iodine ( $^{131}\text{I}$ ) iobenguane, and issued a recommendation on their marketing authorisations.

### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of iodine ( $^{131}\text{I}$ ) iobenguane-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include a new warning on hypertensive crisis and to include hypertension including hypertensive crisis as a new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.

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.

#### **6.3.11. Isotretinoin (NAP) - PSUSA/00001795/201505**

---

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

### **Background**

Isotretinoin is a retinoid compound and a vitamin A derivative that is a stereoisomer of all-trans retinoic acid (tretinoin). It is indicated for the oral treatment of severe forms of acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy. It should not be used for the treatment of prepubertal acne and is not recommended in children less than 12 years of age.

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

### **Summary of recommendation(s) and conclusions**

---

<sup>29</sup> 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

- Based on the review of the data on safety and efficacy, the risk-benefit balance of isotretinoin-containing medicinal products in the approved indications remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAHs should provide separate cumulative reviews of vaginal haemorrhage, erectile dysfunction, tinnitus and deafness and propose amendments to their product information as applicable. In addition, the MAHs should provide detailed reviews on compliance with and the effectiveness of the pregnancy prevention programme (PPP) for each medicinal product (including the generics) presented in a standard way that is consistent with the PPP reports for the innovator product. An overview of the materials that support the PPP and the information on their distribution should be provided by all MAHs, which should be broken down by member state. Furthermore, all MAHs should comment on whether their existing PPP educational materials provide up-to-date information particularly regarding the effectiveness of contraceptive measures. Consideration should be given to whether these materials could be further improved in order to deliver a consistent message and avoid confusion in the target audience. Finally, the MAHs should review their product information regarding neuropsychiatric adverse reactions including depression and suicidal behaviour to ensure the information is provided in a clear, consistent and comprehensive manner.

The frequency of PSUR submission should be revised from three-yearly to 18-monthly 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.

### 6.3.12. Milnacipran (NAP) - PSUSA/00002063/201504

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

#### **Background**

Milnacipran is an inhibitor of serotonin (5-HT) and norepinephrine reuptake indicated for the treatment of depression.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of milnacipran-containing medicinal products in the approved indications remains unchanged.



- Nevertheless, the product information should be updated to include Stevens–Johnson syndrome as a new undesirable effect with a not known frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>30</sup>.
- In the next PSUR, the MAHs should provide a detailed review of reported cases of hyperprolactinemia with milnacipran, including serious and non-serious CIOMS cases. The clinical symptoms, chronology and confounding factors should be clearly presented as well as prolactin blood levels before and after milnacipran treatment if available. The MAHs should also explain on what basis hyperprolactinemia is listed in the current US product information.

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

### 6.3.13. Oxaliplatin (NAP) - PSUSA/00002229/201504

---

Applicant: various

PRAC Lead: Corinne Féchant

Scope: Evaluation of a PSUSA procedure

#### **Background**

Oxaliplatin is an antineoplastic drug belonging to a class of platinum-based compounds. Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of the primary tumour and for the treatment of advanced/metastatic colorectal cancer.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of oxaliplatin-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include as new undesirable effects hypersensitivity vasculitis, and autoimmune pancytopenia with an unknown frequency, and to amend the description of allergic reaction by including the risk of delayed hypersensitivity. Therefore the current terms of the marketing authorisation(s) should be varied<sup>31</sup>.
- In the next PSUR, the MAHs should closely monitor cases of cardiomyopathy, cardiac failure, cardiac arrhythmia, ischaemic heart disease, cerebrovascular disorders, unlisted hepatic events occurring in patient with tumour-free healthy liver tissue, leukaemia, adverse reactions that occurred in the context of intra-arterial

---

<sup>30</sup> 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

<sup>31</sup> 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

chemotherapy/chemoembolisation and hyperthermic intraperitoneal chemotherapy. In addition, the MAHs should discuss the impact of oxaliplatin on the autonomous nervous system (ANS) and the need to update the oxaliplatin product information accordingly. The MAHs should also provide reviews for cases of cholangitis, tumour lysis syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported with oxaliplatin. Moreover, the MAHs should provide a detailed review of pregnancy cases together with literature search on the risk of oxaliplatin exposure during pregnancy. The analysis should be provided in accordance with the 'Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data' ([EMA/CHMP/313666/2005](#)). The MAHs should also provide a review of hemophagocytic syndrome when oxaliplatin has been used by peritoneal administration (off-label use) and consider whether the product information should be updated accordingly.

- The MAHs which have an RMP in place should be requested in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP to review the table of safety concerns. In addition the following safety concerns could not be considered as important potential risks and should be reviewed at an upcoming regulatory procedure affecting the RMP: patients with a history of allergic reaction to the active substance or to any of the excipients, extravasation, neurological toxicity, patient with acute laryngopharyngeal dysaesthesia, neurological symptoms- paresthesia, dysesthesia, sensory neuropathy, gastrointestinal toxicity, mucositis/stomatitis, pulmonary toxicity, abnormal liver function test results or portal hypertension.

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

#### **6.3.14. Pamidronate (NAP) - PSUSA/00002269/201505**

---

Applicant: various

PRAC Lead: Menno Van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

Pamidronate is a nitrogen-containing bisphosphonate, used to prevent osteoporosis. It is indicated for patients with conditions associated with increased osteoclast activity, predominantly lytic bone metastases and multiple myeloma, tumour-induced hypercalcemia and Paget's disease of the bone.

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

##### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of pamidronate-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include in the 'Posology and method of administration' section that patients treated with pamidronate should be given the package leaflet and the patient reminder card, to reflect the current knowledge on osteonecrosis of the jaw as set out in the warnings and undesirable effects sections. Therefore the current terms of the marketing authorisation(s) should be varied<sup>32</sup>. See also 'PRAC recommends further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine' ([EMA/169618/2015](https://www.ema.europa.eu/en/press/news/2015/06/15/prac-recommends-further-measures-to-minimise-risk-of-osteonecrosis-of-the-jaw-with-bisphosphonate-medicine)).
- In the next PSUR, the MAHs should closely monitor further literature and cases of optic neuritis. The MAHs should discuss all available data and also discuss possible mechanism(s) as well as the background incidence of optic neuritis and re-discuss this topic in the next PSUR.
- The MAHs which have an RMP in place should be requested to submit to the national competent authorities (NCAs), within 60 days, a revised RMP to reflect the addition of a new risk minimisation measure (introduction of the reminder card on ONJ) as well as to propose indicators to measure the effectiveness of this new measure.

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.

### 6.3.15. Ticlopidine (NAP) - PSUSA/00002952/201505

---

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ticlopidine is a platelet aggregation inhibitor indicated for the reduction of the risk of first and recurrent stroke, the prevention and correction of platelet function disorders caused by extracorporeal circuits (surgery with extracorporeal circulation, chronic haemodialysis), prevention of subacute occlusions following coronary stent implantation and prevention of major ischemic accidents, particularly coronary, in patients presenting with chronic arterial disease of the lower limbs at the stage of intermittent claudication.

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

#### **Summary of recommendation(s) and conclusions**

- Based on the review of the data on safety and efficacy, the risk-benefit balance of ticlopidine-containing medicinal products in the approved indications remains unchanged.

---

<sup>32</sup> Update of SmPC sections 4.2, 4.4, 4.5 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

- Nevertheless, the product information should be updated to include a warning on an increased bleeding risk when ticlopidine is used concomitantly with selective serotonin reuptake inhibitors and with pentoxifylline in the 'Interaction with other medicinal products and other forms of interaction' section. Therefore the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.
- In the next PSUR, all the MAHs should discuss the risk of serotonergic effects due to increased exposure to tramadol as a consequence of pharmacokinetic (PK) interaction as a new safety signal associated with ticlopidine. An assessment of the data should be provided as well as a conclusion justifying whether the product information should be amended accordingly or not. All the MAHs should closely monitor the adverse drug reaction 'interstitial lung disease' and provide a cumulative review in the next PSUR based on information from clinical trials, spontaneous reports and published literature, with a focus on whether there is sufficient evidence to update the product information. Finally the MAH should submit a detailed review of all available data on the signal of rhabdomyolysis.

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

See also Annex I. 15.4.

### 6.4.1. Gadoversetamide – OPTIMARK (CAP) - EMEA/H/C/000745/LEG 025

---

Applicant: Mallinckrodt Deutschland GmbH

PRAC Rapporteur: Almath Spooner

Scope: MAH's review on data on brain accumulation: relevant literature and any other relevant data source as requested by PRAC as adopted in June 2015

#### Background

Gadoversetamide is a chelate containing gadolinium indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualisation and helps with the characterization of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data (for background, see [PRAC minutes September 2015](#)). The responses were assessed by the Rapporteur for further PRAC advice.

#### Summary of advice/conclusion(s)

- Taking into consideration recently published study results and accumulated knowledge, the PRAC is of the opinion that the issue of accumulation and retention of gadolinium in

---

<sup>33</sup> Update of SmPC section 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

the brain warrants exploration and further coordinated evaluation is needed prior to finalising product information changes for Optimark. The accumulation and retention of gadolinium in the brain is a risk demonstrated in several studies. Therefore the PRAC agreed that an alignment of the safety specifications across the class is considered necessary to reflect the risk of accumulation in the brain and other tissues.

- The MAH should be requested within the next RMP update to include as new important potential risks 'gadolinium accumulation in organs and tissues other than brain tissues' and 'accumulation and retention of gadolinium in the brain', as new missing information 'clinical significance of gadolinium accumulation in organs and tissues other than brain tissues' and 'clinical significance of gadolinium retention in the brain'.

## 7. Post-authorisation safety studies (PASS)

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>34</sup>

See also Annex I. 16.1.

#### 7.1.1. Chlormadinone acetate, ethinyl estradiol (NAP) – EMEA/H/N/PSP/j/0012.3

Applicant: Gideon Richter, various

PRAC Rapporteur: Valerie Strassmann

Scope: Revised joint PASS protocol (following conclusion of Article 31 referral procedure for combined hormonal contraceptives with CHMP opinion adopted in November 2013) to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE)-containing products

#### **Background**

Chlormadinone acetate (CMA) is a steroidal synthetic progestin that can be used as the progestative component in combined oral contraceptives (COCs). Ethinylestradiol is an oestrogen that can be also used in COCs. A revised protocol for a post-authorisation safety study, to study the risk of venous thromboembolism (VTE) associated with chlormadinone/ethinylestradiol (CMA/EE)-containing products, was submitted to the PRAC by a consortium of MAHs in accordance with the conditions to the marketing authorization included in the EC decision [Annex IV](#) for the referral under Article 31 of Directive 2001/83/EC ([EMA/607314/2013](#)) for combined hormonal contraceptives. For further background, see [PRAC minutes May 2014](#), [PRAC minutes April 2015](#) and [PRAC minutes September 2015](#).

#### **Endorsement/Refusal of the protocol**

- The PRAC, having considered the joint updated draft protocol version 1.6 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the PASS study for the above listed medicinal products.

#### 7.1.2. Valproate (NAP) - EMEA/H/N/PSP/j/0029.1

Applicant: Sanofi Aventis R&D, various

<sup>34</sup> In accordance with Article 107n of Directive 2001/83/EC

PRAC Rapporteur: Sabine Straus

Scope: Revised joint PASS protocol for a drug utilisation study (DUS) to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate

### **Background**

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

A revised protocol for a post-authorisation safety study (drug utilisation study) to assess the effectiveness of the risk minimisation measures and to further characterise the prescribing patterns for valproate was submitted to the PRAC by a consortium of MAHs in accordance with conditions to the marketing authorisation included in the EC decision [Annex IV](#) for the referral under Article 31 of Directive 2001/83/EC ([EMA/612389/2014](#)) for valproate-containing medicines. For further background, see [PRAC minutes July 2015](#) and [PRAC minutes September 2015](#).

### **Endorsement/Refusal of the protocol**

- The PRAC, having considered the joint draft protocol version 3.1 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for the PASS study for the above listed medicinal products.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>35</sup>**

See also Annex I. 16.2.

### **7.2.1. Aflibercept – EYLEA (CAP) - EMEA/H/C/002392/MEA/015**

---

Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: PASS protocol for study 18218: assessment of the safety and drug utilisation of intravitreal Eylea in real world clinical practice

### **Background**

Aflibercept (Eylea) is a recombinant fusion protein indicated<sup>36</sup> for the treatment of neovascular (wet) age-related macular degeneration (AMD), of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) as well as for the treatment of visual impairment due to diabetic macular oedema (DME).

As part of the RMP for Eylea and in response to a CHMP request, the MAH was requested in 2012 to conduct a PASS in order to assess the safety and real-life treatment practice in patients with wet age-related macular degeneration, including the potential risk of arterial thromboembolic and cerebrovascular events (ATEs). The MAH submitted a draft protocol for the PASS programme 18128, including two studies to assess the safety of aflibercept, and a

---

<sup>35</sup> 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

<sup>36</sup> As a solution for injection

drug utilization of intravitreal aflibercept in real world clinical practice. The aims of this PASS programme, as proposed, were to monitor the incidence, frequency and severity of ocular and non-ocular adverse events in patients with macular diseases treated with intravitreal aflibercept in the real world clinical setting, and to monitor the drug utilization of intravitreal aflibercept in terms of injection frequency and proportion of bilateral treatment. The PRAC was requested to provide advice to CHMP on the protocol for the PASS programme submitted by the MAH. For background information, see [PRAC minutes October 2014](#), [PRAC minutes March 2015](#) and [PRAC minutes November 2015](#) on the signal of higher systemic exposure compared to ranibizumab after intravitreal injection.

### Summary of advice

- The PRAC discussed the draft protocol for the PASS programme submitted by the MAH and reviewed the cumulative experience gained with the use of intravitreal (IVT) vascular endothelial growth factor (VEGF) inhibitors including aflibercept.
- Taking into account the totality of the data now available post authorisation, as outlined within this procedure as well as within the evaluation of the signal of higher systemic exposure compared to ranibizumab after intravitreal injection, the PRAC was of the view that further re-assurance had been obtained with regards to the systemic safety of the drug class of IVT VEGF inhibitors. However, given that some uncertainties remain, the PRAC concluded that the risk of ATEs should be kept as an important potential risk in the RMP and noted that several studies are ongoing which may provide further data to inform this safety concern. Proposals for PASS designs to further elucidate the risk of ATEs with Eylea were reviewed. Proposals from the MAH were considered unsatisfactory, including the timelines. The PRAC furthermore discussed as an alternative design a retrospective healthcare database study but was concerned by some limitations of the study setting leading to question the interpretability of the results.
- The PRAC concluded by a majority decision (30 positive out of 35 votes, Norway supporting the majority) that the current PASS proposals were unlikely to provide meaningful results with a substantial impact on the understanding of the risk of ATEs for Eylea and on which regulatory action could be justified. In light of this and of the accumulating data, the PRAC concluded that the previously agreed category 3 PASS was no longer justified. The PRAC also concluded that the MAH should continue to monitor the safety of Eylea in PSURs. In particular, the MAH is requested in the context of the next PSUR (DLP: 08/02/2016) (PSUSA/00010020/201511) to review the cumulative evidence with regards to systemic safety and especially ATEs including data from the scientific literature such as the meta-analysis performed by *Schmid et al.*<sup>37</sup> and to discuss any potential changes to the product information as applicable.

### 7.3. Results of PASS imposed in the marketing authorisation(s)<sup>38</sup>

None

---

<sup>37</sup> Schmid M.K., Bachmann L.M., Fäs L., Kessels A.G., Job O.M., Thiel M.A.; Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis.; Br J Ophthalmol. 2015 Feb;99(2):141-6.

<sup>38</sup> In accordance with Article 107p-q of Directive 2001/83/EC

## 7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>39</sup>

See also Annex I. 16.4.

### 7.4.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0807 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0807 (without RMP)

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Submission of final results of the non-interventional (NIS) aliskiren study SPP100A2418 (or A2413) on the incidence of colorectal hyperplasia and gastrointestinal cancer in aliskiren treated patients

#### Background

Rasilez and Rasilez HCT are centrally authorised medicines containing aliskiren, an orally active, non-peptide, potent and selective direct inhibitor of human renin, indicated for the treatment of essential hypertension in adults.

The MAH committed to perform a non-interventional PASS: study SPP100A2418, a cohort study based on use of secondary healthcare claims data as listed in the RMP. The Rapporteur assessed the final results of study SPP100A2418, a cohort study looking at the incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States.

The PRAC discussed the final results from study SPP100A2418, the comprehensive review of the available data related to aliskiren and colorectal hyperplasia and gastrointestinal (GI) cancer provided by the MAH as well as the MAH's responses to the request for supplementary information adopted in September 2015.

#### Summary of advice

- The PRAC agreed that the results of this PASS did not demonstrate a statistically meaningful difference between aliskiren and other antihypertensives or between aliskiren and non-hypertensives for GI cancer. It is possible that these comparisons were not adequately powered to detect significant differences in risks given the smaller number of aliskiren users.
- With regard to the risk of colorectal hyperplasia, the risk was higher in the aliskiren cohort as well as in the antihypertensive cohort, when compared to the non-hypertensive cohort. The overall relative risk of colorectal hyperplasia for all patients exposed to aliskiren versus all patients exposed to antihypertensive drugs other than aliskiren was statistically significant (1.08 (95% CI: 1.05, 1.11)) but was not significant among incident antihypertensive therapy patients exposed to aliskiren versus patients exposed to antihypertensive drugs other than aliskiren (1.03 (95%CI: 0.92, 1.15)). The PRAC also noted that, although hazard ratios were adjusted for the different potential confounders measured in the study database, the age of patients was not equally represented across the cohorts. Also several limitations due to the database used for the research were noted by the PRAC. The overview of evidence from clinical

---

<sup>39</sup> 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



trials, safety studies, and published observational studies provided by the MAH also suggests that the risk of colorectal hyperplasia is similar among antihypertensive users or placebo users.

- The PRAC supported the MAH's conclusions that no changes to the product information of aliskiren-containing products are warranted at this stage. The PRAC agreed that data from non-interventional multi-database cohort study SPP100A2417, to assess the incidence rates of colorectal hyperplasia among hypertensive patients (expected January 2016) and from the clinical study ATMOSPHERE (expected Q3-Q4 2016) will contribute significantly to the presently accrued data and will enable further characterization of this potential risk.

### **7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>40</sup>**

See Annex I. 16.5.

### **7.6. Others**

See Annex I. 16.6.

### **7.7. New Scientific Advice**

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

### **7.8. Ongoing Scientific Advice**

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

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

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

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

### **8.1. Annual reassessments of the marketing authorisation**

See Annex I. 17.1.

### **8.2. Conditional renewals of the marketing authorisation**

See Annex I. 17.2.

---

<sup>40</sup> In line with the revised variations regulation for any submission before 4 August 2013

### 8.3. Renewals of the marketing authorisation

See Annex I. 17.3.

## 9. Product related pharmacovigilance inspections

### 9.1. List of planned pharmacovigilance inspections

None

### 9.2. Ongoing or concluded pharmacovigilance inspections

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

## 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. Efavirenz, emtricitabine, tenofovir disoproxil – ATRIPLA (CAP) - EMEA/H/C/000797/WS/0792
- elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP) - EMEA/H/C/002574/WS/0792
- emtricitabine – EMTRIVA (CAP) - EMEA/H/C/000533/WS/0792
- emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP) - EMEA/H/C/002312/WS/0792
- emtricitabine, tenofovir disoproxil – TRUVADA (CAP) - EMEA/H/C/000594/WS/0792
- tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS/0792

Applicant: Bristol-Myers Squibb and Gilead Sciences Ltd., Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.4 of the SmPC in order to delete the human immunodeficiency virus (HIV) class label wording for mitochondrial dysfunction following the review of existing data on mitochondrial toxicity including the Mitochondrial Toxicity in Children (MITOC) study. The Package Leaflets for Viread, Truvada and Emtriva are updated accordingly

#### Background

Combination antiretroviral therapy (cART) consists of any combination regimen of antiretroviral medicines that include nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), with non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) or integrase inhibitors for the treatment of patients affected by the human immunodeficiency virus (HIV-1).

In the context of the ongoing procedures initiated in July 2014 reviewing new evidence with respect to mitochondrial toxicity, lactic acidosis and lipodystrophy associated with antiretroviral medicines, the impact on the product information is under review. The PRAC concluded the review on lactic acidosis and lipodystrophy in October 2015 and provided advice to the CHMP. For further background, see [PRAC minutes October 2015](#).

In the context of the evaluation of a type II variation procedure on the review of the existing data on mitochondrial toxicity including results from the Mitochondrial Toxicity in Children (MITOC) study, the CHMP requested PRAC advice.

#### Summary of advice

- Based on the review of the available information, the PRAC considered that further information was needed by means of a request for supplementary information (RSI) before concluding its advice to CHMP. The PRAC will be further consulted in March 2016.

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

None

## 10.3. Other requests

### 10.3.1. Human thrombin<sup>41</sup> – FLOSEAL HAEMOSTATIC MATRIX (FLOSEAL V/H SD<sup>42</sup>) (medical device); HEMOBLAST HAEMOSTATIC AGENT (medical device); SURGIFLO HAEMOSTATIC MATRIX KIT (medical device)

---

Applicant: Baxter AG; Biom' Up; Ferrosan A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: PRAC consultation on the potential applicability of the recommendation of the signal of intestinal obstruction with human fibrinogen/human thrombin (TachoSil) (EPITT 18373) to Floseal V/H SD; Hemoblast Haemostatic Agent; Surgiflo Haemostatic Matrix Kit

#### Background

Human thrombin is a serine protease used as a plasma-derived ancillary medicinal substance in some medical devices such as Floseal V/H SD to increase the haemostatic effect when the device is applied topically during surgery to a bleeding site as an adjunct to haemostasis, when control of bleeding by ligation or other conventional procedures is ineffective or impractical.

Further to the assessment of the signal of intestinal obstruction associated with TachoSil (human fibrinogen, human thrombin), the PRAC recommended updating the product information to include new warnings to minimise the risk of gastrointestinal obstruction; updating the RMP accordingly and the distribution of a direct healthcare professional communication (DHPC). For further background, see [PRAC minutes December 2015](#). During signal detection activities, the EMA identified in EudraVigilance three cases of intestinal obstruction, as well as 3 cases in a publication on Floseal V/H SD.

In line with the [Directive 93/42/EEC](#) on medical devices, the relevant medicines competent authority (i.e. CHMP for Floseal V/H SD) should provide the notified body with advice on any information that can impact on the established benefit/risk profile of the medical device containing the ancillary medicinal substance to be considered in the framework of a conformity assessment procedure. The CHMP requested PRAC advice.

#### Summary of advice

---

<sup>41</sup> As an ancillary medicinal substance

<sup>42</sup> Vapor heated, solvent/detergent treated

- Based on the evidence in the literature and EudraVigilance, the PRAC concluded that intestinal obstruction may occur in association with the administration of FloSeal. Therefore, the PRAC advised including 'small bowel obstruction' and 'foreign body reaction with giant cell granulomas' as undesirable effects in the listings provided in the instructions for use of FloSeal to highlight these possible risks and complement the information already included (i.e. allergic response, adhesion formation, inflammation). This advice is also applicable to Hemoblast Haemostatic Agent and Surgiflo Haemostatic Matrix Kit when used in abdominal surgery, based on similar composition and mode of action.

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

### 11.1. Safety related variations of the marketing authorisation

#### 11.1.1. Cyproterone acetate, ethinylestradiol (NAP) - NL/H/xxxx/WS/150

Applicant: Bayer (Diane-35 and generics)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a variation procedure evaluating the first interim report of the joint database drug utilisation study (DUS) on the use of cyproterone acetate/ethinylestradiol (CPA/EE) and based on the protocol approved by the PRAC in April 2015, as per the conclusions of the referral procedure under Art 107i of Directive 2001/83/EC (EMEA/H/A-107i/1357) finalised in 2013

#### Background

Cyproterone acetate (CPA) is a synthetic steroidal antiandrogen, progestin and antigonadotropin and is used in combination with ethinylestradiol (EE), a steroidal estrogen, for the treatment of moderate to severe acne and/or for hirsutism in women of reproductive age.

In 2013, a safety referral procedure under Article 107i of Directive 2001/83/EC on cyproterone- and ethinylestradiol-containing medicines ([EMEA/H/A-107i/1357](#)) was concluded. In addition to changes to the product information, the distribution of educational materials to prescribers and patients to minimise the risk of venous thromboembolism (VTE), the MAHs were requested to conduct drug utilisation and post authorisation safety studies.

In the context of an ongoing variation evaluating the interim results of the drug utilisation study (DUS) on the use of CPA/EE in three European countries, the Netherlands as Reference Member States (RMS) for the originator medicinal product requested PRAC advice. The DUS will compare user characteristics of 2011-2012 with 2014 (i.e. before and after the finalisation of the referral procedure). The current interim report comprises the user characteristics of 2011-2012. These results of the 2014 comparison will be delivered when those data are available, in 2016.

#### Summary of advice

- The PRAC agreed with the draft assessment and conclusion of the RMS that limited information on acne diagnosis, diagnoses of other hyperandrogenic conditions,

menstrual problems or general practitioners (GP) consultations for contraceptive management or recent acne treatment was observed in two of the three databases, which might be due to underreporting. In the third database, the majority of CPA/EE users had a recent record of acne diagnosis or treatment. Concomitant use of CPA/EE and other hormonal contraceptives was observed for a small proportion of users.

- The PRAC highlighted the importance of gathering as much information as possible on the diagnosis for the new users of CPA/EE in the final study report.

## 11.2. Other requests

None

## 12. Organisational, regulatory and methodological matters

### 12.1. Mandate and organisation of the PRAC

None

### 12.2. Coordination with EMA Scientific Committees or CMDh

#### 12.2.1. Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population

---

PRAC lead: Jolanta Gulbinovič; Amy Tanti

Following the December 2015 presentation (see [PRAC minutes December 2015](#)), the section of the guideline dedicated to off-label use was further amended and presented to PRAC for discussion. It was suggested to further amend it as well as other parts of the document. The revised draft guideline will be presented to PRAC in March/April 2016.

#### 12.2.2. Paediatric Committee (PDCO) - paediatric pharmacovigilance: organ maturation tables

---

The EMA Secretariat presented to the PRAC the project on the organ maturation tables tool developed to ensure better use of EudraVigilance (EV) queries/data for medicines used in the paediatric population, taking into account that adverse drug reactions (ADR) in adults and children may be different and this different susceptibility may relate to the immaturity of most organs. The tables are aiming at identifying possible ADRs that are maturation related. The methodology was presented together with the standard EV paediatric (SEVP) query tool and some examples of analyses. To date, organ maturation tables of the liver, kidney, lung, gastro-intestinal (GI) tract and brain exist. The use of the tables may increase once the existing work, including the methodology has been published. The PRAC welcomed the update on this interesting scientific work and wished to be kept informed of progress in utilising the tool.

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

### **12.3.1. Advisory group on classification of post-authorisation studies (CPAS) to the marketing authorisations**

---

The EMA Secretariat presented to the PRAC a newly established advisory group at EMA on classification of post-authorisation studies (CPAS), responsible for providing advice to CHMP/PRAC and EMA on potential Annex II imposed post-authorisation studies in order to improve the consistency in their classification, wording and EMA Committees' involvement in the follow-up of protocols and final study results. The CPAS also aims to look into the classification of post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES) where both safety and efficacy data are required/expected to be collected, and into the main area of concern determining the obligation. Proposed criteria were discussed in order to involve PRAC in the assessment of PAES and observational PASS. The CPAS will further define criteria and will be involved in advance of any CHMP and PRAC discussion on conditions for imposing a PAS. Follow-up discussion will take place in due course.

### **12.3.2. Guideline on safety and efficacy follow-up – risk management plans for ATMPs**

---

The EMA Secretariat informed the PRAC of the European Commission's request to revise the current 'Guideline on safety and efficacy follow-up – risk management plan of advanced therapy medicinal products (ATMPs)' ([EMEA/149995/2008](#)). Following a call for interest launched amongst PRAC, it was confirmed that Julie Williams and Brigitte Keller-Stanislawski will join the dedicated drafting group which is also composed of EMA, CAT and CHMP members. Follow-up will be given in due course.

## **12.4. Cooperation within the EU regulatory network**

### **12.4.1. EMA review of seasonal influenza vaccines enhanced safety surveillance systems**

---

Following the adoption and entry into force in 2014 of the 'interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' ([EMA/PRAC/222346/2014](#)), the 2014/2015 campaign of vaccination was the first season in which its requirements were implemented, during which there was no strain change. As the 2015/2016 season will include new strains, a new enhanced passive surveillance approach and real world testing of the common MAHs' surveillance plans will apply. Therefore, the EMA proposed to review the process and identify lessons learned so far. More precisely, this EMA initiative aims at reviewing the implementation of the guidance requirements on enhanced safety surveillance for seasonal influenza vaccines in the EU by the MAHs (CAPs and NAPs), highlighting the challenges and, if readily apparent, to propose improvements for both the regulatory process and guidance requirements as well as sharing the results with the PRAC and the network. The EMA plans to share its results with PRAC in Q3-Q4 2016. The PRAC strongly supported the initiative and wished to be kept informed of progress.

### **12.4.2. EMA reflection paper on extrapolation across age groups**

---

PRAC lead: Jolanta Gulbinovič

At the organisational matters teleconference held on 28 January 2016, the EMA secretariat presented to the PRAC an update on the EMA initiative to develop a regulatory framework for extrapolation across age groups to ensure a consistent and harmonised review of extrapolation approaches across the medicinal product development life cycle. The European extrapolation network follows a multidisciplinary approach including experts from relevant Committees, including a PRAC representative, and Working Parties. The PRAC was presented with an outline of the consolidated EMA extrapolation reflection paper, with specific points for PRAC consideration, in particular, handling of uncertainties and assumptions at a planning stage. The adoption of the reflection paper is planned for March 2016 at the level of the PRAC before the organisation of a workshop in May 2016.

## **12.5. Cooperation with International Regulators**

None

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

None

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2016**

---

At the plenary meeting and at the organisation matters teleconference held on 28 January 2016, the EMA secretariat presented a draft of the 2016 PRAC work plan. Final adoption is planned at the February 2016 PRAC meeting.

## **12.8. Planning and reporting**

None

## **12.9. Pharmacovigilance audits and inspections**

### **12.9.1. Pharmacovigilance systems and their quality systems**

---

None

### **12.9.2. Pharmacovigilance inspections**

---

None

### **12.9.3. Pharmacovigilance audits**

---

None

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

### **12.10.1. Periodic safety update reports**

---

None

### **12.10.2. Granularity and Periodicity Advisory Group (GPAG)**

---

PRAC lead: Menno van der Elst; Margarida Guimarães

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

### **12.10.3. PSUR action group - roadmap for PSUR issues: scoping paper as a basis for the workshop in January 2016**

---

PRAC lead: Almath Spooner; Jolanta Gulbinovic; Margarida Guimarães; Menno van der Elst

Following the October and December 2015 discussions (see [PRAC minutes October 2015](#) and [PRAC minutes December 2015](#)), the PRAC agreed the content of the scoping paper for the PRAC/CMDh drafting group workshop organised in January 2016. This workshop was composed of EMA staff, PRAC and CMDh delegates, with the aim of supporting a common understanding relating to PSUSAs procedures for nationally approved products (NAPs) only.

### **12.10.4. PSUR/PSUSA – guidance on handling of EU single PSUR procedures for suspended or withdrawn/non-renewed/revoked marketing authorisations**

---

At the organisational matters teleconference held on 28 January 2016, the EMA secretariat presented to the PRAC a draft guidance document on the handling of PSUR/PSUSA procedures for suspended, withdrawn, non-renewed or revoked marketing authorisations (MAs). The PRAC discussed the proposals for each scenario and the related transparency measures. The EMA will further revise the guidance taking into consideration PRAC comments and a revised version will be presented in due course.

### **12.10.5. PSURs repository – update on post-audit requirements**

---

At the organisational matters teleconference held on 28 January 2016, the EMA secretariat presented an update on the PSUR repository and post-audit requirements. The pilot on the use of the repository has been running since February 2015. Following a written consultation with national competent authorities, it was agreed to move the use of the repository from the 'pilot' to a 'switch on' phase, meaning that the use of the full functionalities of the repository is mandatory for the network as of 11 February 2016. On 13 June 2016, the use of the PSUR repository becomes mandatory for all stakeholders.

### **12.10.6. Union reference date list – consultation on the draft list**

---

The PRAC endorsed the draft revised EURD list version December 2015 reflecting the PRAC comments impacting on the DLP and PSUR submission frequencies of the substances/combinations.



The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting in January 2016, the updated EURD list was adopted by the CHMP and CMDh at their January 2016 meetings and published on the EMA website on 04/02/2016, see:

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

## **12.11. Signal management**

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

---

PRAC lead: Sabine Straus

At the organisational matters teleconference held on 28 January 2016, the PRAC was updated on the outcome of the January 2016 SMART Working Group (SMART WG) work stream (WS) 1. The SMART WS1 discussed the planned revision of GVP Module IX on Signal Management. The draft updated GVP module IX, once further consolidated, will be presented to the PRAC in March/April 2016 for agreement before release for public consultation. In addition, the PRAC was updated on SMART WS1 discussions on the applicability of PRAC recommendations on signals to homeopathic products. In addition, the PRAC was updated on the SMART WG WS 2-3 main activities, in particular, work on the preparation of an addendum to GVP module IX on 'Methodological aspects of signal detection from spontaneous reports'. This addendum will capture principles relevant to both national competent authorities and MAHs and will not be focused on EudraVigilance any longer. All remaining practicalities (e.g. how to use the electronic reaction monitoring reports (eRMR) tool) and detailed recommendations (prioritisation/thresholds) for signal detection will then be captured in a more practical document on how to screen EudraVigilance.

## **12.12. Adverse drug reactions reporting and additional reporting**

### **12.12.1. Management and reporting of adverse reactions to medicinal products**

---

None

### **12.12.2. Additional monitoring**

---

None

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

---

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 27/01/2016 on the EMA website (see: [Home>Human Regulatory>Human](#)

## **12.13. EudraVigilance database**

### **12.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement project update**

---

The EMA Secretariat updated the PRAC on the EudraVigilance (EV) auditable requirement project, in particular the 'EV audit checklist for technical implementation of the EV auditable requirement functionalities' presented in December 2015. The checklist was endorsed by the PRAC following some minor refinements. In addition, the PRAC endorsed the nomination of Jean-Michel Dogné (BE) and Edurne Lazaro (ES) as technical advisers in the tender process to the company that will perform the audit of the EV system in August 2016. Finally, the PRAC was consulted on the EV training plan detailing the training curriculum to support the enhancements in EV and the key documentation that will be released to prepare stakeholders (national competent authorities, MAHs and sponsors of clinical trials) for the changes taking place in the EV system. The PRAC was presented with the training approach that will include in particular support via e-learning sessions and guidance documentation. Following further consultations and adoption by the [European Risk Management Strategy Facilitation Group](#) (ERMS-FG), the training plan will be published on the EMA website, with a target date in March 2016. The PRAC will be updated on the ongoing activities related to confirmation of full EV functionality on a regular basis.

## **12.14. Risk management plans and effectiveness of risk minimisations**

### **12.14.1. Risk management systems - Summaries of risk management plans (RMP): update**

---

Following the September 2015 discussion on the preliminary analysis of the 1-year pilot phase on the publication of RMP summaries (see [PRAC minutes September 2015](#)), the EMA Secretariat informed the PRAC that the pilot had come to an end. In the light of the experience gathered during the pilot, improvements have been made to the template and process for preparing the summaries, to better meet the needs and expectations of stakeholders who have expressed an interest in RMP summaries. The revision of the RMP summary template has been done in parallel to the revision of the full RMP template and will go imminently for public consultation together with the revised GVP Module V on Risk management systems. The new RMP summary template has been improved, simplified and further contextualised in order to meet expectations from the different audience groups. The revised summaries have been carefully designed to follow plain-language principles to facilitate readability by the general public. Plain-language principles include organising information logically, giving priority to action points, breaking information into digestible parts, and using a layout that improves readability. The publication of RMP summaries in the format used during the pilot phase will cease for new medicines which receives a CHMP opinion from January 2016 onwards. The new summaries will gradually start being produced once the new RMP template is finalised (after the public consultation). In the meantime, information on RMPs will continue to be made publicly available in CHMP assessment reports, which are published as part of the [European public assessment reports](#) (EPARs) for each medicine centrally authorised.

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

None

### **12.15. Post-authorisation safety studies (PASS)**

#### 12.15.1. Post-authorisation Safety Studies – imposed PASS

None

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

None

### **12.16. Community procedures**

#### 12.16.1. Referral procedures for safety reasons

None

### **12.17. Renewals, conditional renewals, annual reassessments**

None

### **12.18. Risk communication and transparency**

#### 12.18.1. Public participation in pharmacovigilance

None

#### 12.18.2. Safety communication

None

### **12.19. Continuous pharmacovigilance**

#### 12.19.1. Incident management

None

### **12.20. Others**

#### 12.20.1. Initial marketing authorisation(s) - revised accelerated assessment procedural timetables

PRAC lead: Ulla Wändel Liminga

Following the discussion in December 2015 (see [PRAC minutes December 2015](#)) and further discussion in January 2016 at the level of the CHMP, the EMA presented to the PRAC an updated proposal for a revised procedural timetable for the evaluation of marketing authorisation applications under accelerated assessment. Following comments, and in order

to address these, follow-up discussion are planned at the January 2016 CHMP and February 2016 PRAC meetings.

### 12.20.2. Pharmacovigilance operation and implementation - proposal for a streamlined governance structure

---

The EMA Secretariat presented to the PRAC a proposal to review and streamline the EU network governance structure for pharmacovigilance implementation and operation and outlined the role of the PRAC on the proposed governance of operational aspects. Following the implementation of main outputs as planned, it was highlighted that most work now relates to operation and continuous improvement of the EU pharmacovigilance system.

While the PRAC welcomed this timely proposal, three areas of focus emerged during the discussion: first, the capacity of the Committee's schedule (monthly meeting and ORGAM teleconference), secondly, the support resource requirements for such a transfer of work from the current Implementation Group and Project and Maintenance Groups (PMG) to PRAC, and thirdly the different roles needed for PRAC to advise on implementation tasks compared with its scientific advisory function, and the appropriate accountabilities. The oversight and tracking of implementation deliverables was recognised to be important. In conclusion the PRAC supported making progress on this discussion via further consideration of the options before finalising a recommendation to the Heads of Medicines Agencies ([HMA](#)).

Further discussion at the level of the European Risk Management Strategy Facilitation Group ([ERMS-FG](#)) and at the February 2016 PRAC are scheduled in order to adopt the proposed new structure before presentation at HMA later in February 2016 for agreement.

### 12.20.3. Strategy on measuring the impact of pharmacovigilance activities

---

Following the last discussion in December 2015 (see [PRAC minutes December 2015](#)) and consolidation of the document, the PRAC adopted its 'strategy on measuring the impact of pharmacovigilance activities' ([EMA/790863/2015](#)). The strategy details the way to gather data and knowledge on the concrete effect of measures and processes meant to ensure the safe use of medicines for patients in the EU. It focusses on four areas: measuring the effectiveness of risk minimisation measures on specific products; measuring the effect of specific pharmacovigilance processes (e.g. spontaneous reporting of suspected adverse reactions, signal management); investigating how to ensure engagement of key stakeholders (e.g. patients, healthcare professionals) as well as further improving methodologies to determine the effect of pharmacovigilance activities on public health. The strategy paper also includes an overview of activities and deliverables for implementation, with a high-level overview of the strategy's objectives for the next three years as well as a detailed work plan for 2016. PRAC nominations have been received to participate in the interest group (IG). Follow-up discussion is planned for the February 2016 PRAC meeting to discuss the mandate of the IG.

## 13. Any other business

None

## 14. Annex I – Risk management plans

### 14.1. 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).

#### 14.1.1. Amlodipine, valsartan - EMEA/H/C/004037

---

Scope: Treatment of essential hypertension

#### 14.1.2. Atazanavir - EMEA/H/C/004048

---

Scope: Treatment of human immunodeficiency virus (HIV)-1

#### 14.1.3. Bortezomib - EMEA/H/C/004076

---

Scope: Treatment of multiple myeloma

#### 14.1.4. Selexipag - EMEA/H/C/003774, Orphan

---

Applicant: Actelion Registration Ltd

Scope: Treatment of pulmonary arterial hypertension (PAH)

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

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

#### 14.2.1. Aliskiren – RASILEZ (CAP) - EMEA/H/C/000780/WS/0771 aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP) - EMEA/H/C/000964/WS/0771

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of the RMP with regard to identified risks, missing information, concomitant use of other medicines, drug-drug interactions, removal of safety issues attributed to the withdrawn aliskiren/amlodipine (Rasilamlo) and aliskiren/amlodipine/HCTZ (Rasitrio). The variation is supported by study report SPA100A: antihypertensive effects and long-term safety of aliskiren in elderly patients

#### 14.2.2. Colistimethate sodium – COLOBREATHE (CAP) - EMEA/H/C/001225/II/0021

---

Applicant: Forest Laboratories UK Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of the RMP (version 6.0) in order to add information on the first interim report for study CLB-MD-05 (open-label observational safety study of Colobreathe compared with other inhaled antipseudomonal antibiotics in cystic fibrosis patients using cystic fibrosis registries, MEA 009) and the protocol for study CLB-MD-08 (post authorisation registry based safety study which aims to evaluate the effectiveness of the risk minimisation educational materials, including DVD and patient and healthcare professional guide, implemented in the EU for Colobreathe)

#### 14.2.3. Imatinib – GLIVEC (CAP) - EMEA/H/C/000406/II/0098/G

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP in order to exclude that there is a potential drug interactions with acetaminophen/paracetamol and imatinib, the elderly population as missing information. In addition, the RMP reflects safety actions taken since the last update including drug rash with eosinophilia and system symptoms, gastric antral vascular ectasia and chronic renal failure (from variations EMEA/H/C/000406/II/0090, II/0095 and II/0096). Finally, the due dates for the final study reports of three category 3 studies: CSTI571A2405, CSTI571A2403 and CSTI571L2401 have been amended

#### 14.2.4. Piperaquine tetraphosphate, arteminol – EURARTESIM (CAP) - EMEA/H/C/001199/II/0020

---

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

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP with regard to the delay to start resistance monitoring, collection of off label use data, submission of reports of imposed addition pharmacovigilance activities

#### 14.2.5. Teriparatide – FORSTEO (CAP) - EMEA/H/C/000425/II/0042/G

---

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 4) and submission of a revised protocol for post authorisation safety studies (PASS) B3D-MC-GHBX[2.2] and B3D-MC-GHBX[2.3]. In addition, the RMP has been updated to include non-uraemic calciphylaxis as a potential important risk as requested by PRAC

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

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

#### 14.3.1. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0845 lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0845 lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0845

---

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Update of sections 4.2, 4.3, 4.4 and 5.2 of the SmPC in order to update the safety information to align the hepatic impairment wording of the following abacavir-containing

products: Ziagen, Kivexa, Trizivir with the most recently approved medicinal product Triumeq. The Package Leaflet is updated accordingly

#### **14.3.2. Abiraterone – ZYTIGA (CAP) - EMEA/H/C/002321/II/0036/G**

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope: Grouped variation to submit clinical study reports (CSRs) associated with 4 studies listed in the RMP to address missing information in non-white patients:  
1) study ABI-PRO-3001: phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (JNJ-212082) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy; 2) study 212082PCR3001: open-label study of abiraterone acetate in subjects with metastatic castration-resistant prostate cancer who have progressed after taxane-based chemotherapy; 3) study 212082PCR2007: phase 2 open-label study of abiraterone acetate (JNJ-212082) and prednisolone in patients with advanced prostate cancer who have failed androgen deprivation and docetaxel-based chemotherapy; 4) study JNJ-212082-JPN-102: phase 1 study of JNJ-212082 (abiraterone acetate) in chemotherapy-naïve patients with castration-resistant prostate cancer. In addition, submission of the interim analysis of clinical study report CSR for study ABI-PRO-3002: phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (JNJ-212082) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer is discussed with regards to missing information for use of Zytiga in non-white patients (CSR previously submitted). The RMP (version. 11.0) is updated accordingly, including further changes from other procedures

#### **14.3.3. Atazanavir, atazanavir sulfate – REYATAZ (CAP) - EMEA/H/C/000494/X/0094/G**

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Isabelle Robine

Scope: Line extension for a new pharmaceutical form (oral powder), a new strength for the oral powder presentation (50 mg), and a new paediatric indication (patients from 3 months of age and weighing at least 5kg) grouped with an update of Reyataz capsules in light of new paediatric data. The RMP is also updated to include minor revisions with regard to nephrolithiasis following PRAC's assessment of RMP version 7.3

#### **14.3.4. Ataluren – TRANSLARNA (CAP) - EMEA/H/C/002720/II/0016/G**

---

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.4 to remove precautions for use relating to the co-administration of ataluren with substrates or inducers of UGT1A9 and of section 4.5 of the SmPC to remove statements relating to the potential effect of co-administration of ataluren with inducers or substrates of UGT1A9 and to add results from studies PTC124-GD-026-HV and PTC124-GD-027-HV (MEA 011 and MEA 012). The Package Leaflet is updated accordingly. The RMP (version 4.2) is updated accordingly

#### **14.3.5. Dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/II/0089**

---

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Torbjorn Callreus

Scope: Update of sections 4.4 and 4.9 of the SmPC regarding the availability of the specific reversal agent for dabigatran (Praxbind (idarucizumab)). In addition, the MAH took the opportunity of this procedure to update the coagulation factors in section 4.9. The RMP (version 31.4) including the educational materials, is updated accordingly

#### 14.3.6. Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/II/0045

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Update of section 4.4 of the SmPC based on results from studies CICL670A2425, CICL670A2426 and CICL670AFR01T and patient survey. The Package Leaflet and Annex II are updated accordingly. The RMP (version 11) is updated accordingly

#### 14.3.7. Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/X/0043

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

Scope: Line extension for a new pharmaceutical form and new strengths (Exjade 90, 180 and 360 mg film-coated tablets)

#### 14.3.8. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/X/0022/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Extension of indication to include the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP) in paediatric (age 1 year and above) patients who had an insufficient response to other treatments (e.g. corticosteroids, immunoglobulins). Grouping with the line extension for a new tablet strength (12.5 mg) and a new powder for oral suspension formulation (25 mg)

#### 14.3.9. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0029/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.4 and 4.8 of the SmPC with reference to bone marrow reticulin formation and risk of bone marrow fibrosis and section 5.1 of the SmPC with updated exposure data, based on the final study reports for study TRA112940 (a longitudinal 2-year bone marrow study of eltrombopag olamine (SB-497115-GR) in previously treated adults, with chronic immune (idiopathic) thrombocytopenic purpura (ITP)), and study TRA105325 (EXTEND (Eltrombopag eXTENDED Dosing study) an extension study of eltrombopag olamine (SB-497115-GR) in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP) previously enrolled in an eltrombopag study). As a consequence, Annex II is updated in order to delete 'increased bone marrow reticulin fibres' from the key elements to be included in the educational material. In addition, the MAH took the opportunity to propose an update of the due date in the RMP for the provision of the final clinical study report (CSR) for MEA 022.1 (effectiveness of educational materials for hepatitis C associated thrombocytopenia). The RMP (version 36) is updated accordingly

#### 14.3.10. Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/II/0030

Applicant: Novartis Europharm Ltd



PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of sections 4.5 and 5.2 of the SmPC to reflect the drug-drug interaction with ciclosporin (RAD201583). The Package Leaflet is updated accordingly. The RMP (version 37.0) is updated accordingly

#### 14.3.11. Human normal immunoglobulin – HYQVIA (CAP) - EMEA/H/C/002491/II/0021

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the paediatric population. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly

#### 14.3.12. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0016

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Extension of indication to broaden the existing indication for chronic lymphocytic leukaemia (CLL) to include all previously untreated patients including those with 17p deletion or TP53 mutation based on the results from the final clinical study report (CSR) of study PCYC-1115-CA (MEA 021). As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP (version 5.0) is updated accordingly

#### 14.3.13. Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/II/0017

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.5 of the SmPC in order to amend the clinical recommendations for the co-administration of idelalisib with anticoagulants. The Package Leaflet is updated accordingly

#### 14.3.14. Insulin degludec, insulin aspart – RYZODEG (CAP) - EMEA/H/C/002499/II/0017

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Qun-Ying Yue

Scope: Extension of indication to include the paediatric population from 1 to 18 years of age for Ryzodeg. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly

#### 14.3.15. Insulin degludec, liraglutide – XULTOPHY (CAP) - EMEA/H/C/002647/II/0012

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update the posology and pharmacology information in type 2 diabetes patients with moderate renal impairment

#### 14.3.16. Nintedanib – OFEV (CAP) - EMEA/H/C/003821/WS/0766; VARGATEF (CAP) - EMEA/H/C/002569/WS/0766

---

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Leonidas Klironomos

Scope: Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to include further information related to patients with hepatic impairment based on the clinical study reports (CSR) of studies 1199.37, 1199.39 and 1199.200. The provision of the clinical study report (CSR) of study 1199.200 addresses the post-authorisation measure MEA 001. The RMP (version 2.0) for Ofev and RMP (version 3.0) for Vargatef are updated accordingly

#### 14.3.17. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0002

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment as monotherapy of locally advanced or metastatic non-squamous (NSCLC) after prior chemotherapy in adults based on study CA209057. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, SmPC section 4.8 has been revised with updated combined clinical trial exposure numbers to reflect inclusion of studies in non-squamous NSCLC and in nivolumab in combination with ipilimumab in advanced melanoma. The RMP (version 3.0) is updated accordingly

#### 14.3.18. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0003

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the treatment in combination with ipilimumab of advanced (unresectable or metastatic) melanoma in adults based on interim data from study CA209067 and the final clinical study report (CSR) of study CA209069. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II and Package Leaflet. The RMP (version 3.0) is updated accordingly. Paediatric non-clinical biomarker study is also provided to fulfil paediatric requirements

#### 14.3.19. Nivolumab – OPDIVO (CAP) - EMEA/H/C/003985/II/0008

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on toxic epidermal necrolysis (TEN) and encephalitis. The Package Leaflet is updated accordingly

#### 14.3.20. Ponatinib – ICLUSIG (CAP) - EMEA/H/C/002695/II/0028

---

Applicant: Ariad Pharma Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Update of sections 4.4 and 4.8 of the SmPC with reference to renal artery stenosis. The Package Leaflet is updated accordingly. The RMP (version 13.1) is updated accordingly

#### 14.3.21. Ranibizumab – LUCENTIS (CAP) - EMEA/H/C/000715/II/0059

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 5.1 of the SmPC in order to reflect the information from the long-term clinical studies E2401 and E2402 in retinal vein occlusion (RVO) patients. This addresses the post-authorisation measure MEA 055. The RMP (version 15) is updated accordingly

#### 14.3.22. Sildenafil – XADAGO (CAP) - EMEA/H/C/002396/II/0008

---

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Update of sections 4.5 and 5.2 of the SmPC to introduce information on on sildenafil effects on breast cancer resistance protein (BCRP). The RMP is updated accordingly

#### 14.3.23. Simeprevir – OLYSIO (CAP) - EMEA/H/C/002777/II/0015

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to amend the safety information regarding the use of Olysio in interferon-free regimens, based on the primary analysis (SVR12) of studies HPC3017 and HPC3018. The Package Leaflet and Labelling are updated accordingly

#### 14.3.24. Sitagliptin – JANUVIA (CAP) - EMEA/H/C/000722/WS/0846; RISTABEN (CAP) - EMEA/H/C/001234/WS/0846; TESAVEL (CAP) - EMEA/H/C/000910/WS/0846; XELEVIA (CAP) - EMEA/H/C/000762/WS/0846

---

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update the safety information following completion of TECOS cardiovascular safety study. The RMP (version 6.0) is updated accordingly

#### 14.3.25. Sitagliptin, metformin hydrochloride – EFFICIB (CAP) - EMEA/H/C/000896/WS/0847; JANUMET (CAP) - EMEA/H/C/000861/WS/0847; RISTFOR (CAP) - EMEA/H/C/001235/WS/0847; VELMETIA (CAP) - EMEA/H/C/000862/WS/0847

---

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update the safety information following completion of TECOS cardiovascular safety study. The RMP (version 6.0) is updated accordingly

#### 14.3.26. Sonidegib – ODOMZO (CAP) - EMEA/H/C/002839/II/0001/G

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2 and 5.2 of the SmPC to add information on posology and pharmacology of sonidegib in hepatic impaired patients resulting from study CLDE225A2113 (MEA 006) and update of section 4.5 of the SmPC to add information on drug-drug interaction with proton pump inhibitors (esomeprazole) resulting from study CLDE225A2118 (MEA 007)

#### 14.3.27. Telavancin – VIBATIV (CAP) - EMEA/H/C/001240/II/0023

Applicant: Clinigen Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: Update of section 4.2 and 5.2 of the SmPC and Annex II in order to update the guidelines for obese patients and to remove the reference to pharmacokinetic (PK) obesity study following the assessment of ANX 001.1 post authorisation measure. The Package Leaflet is updated accordingly. The RMP (version 3) is updated accordingly

#### 14.3.28. Ulipristal – ESMYA (CAP) - EMEA/H/C/002041/II/0037

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information based on the results of phase III study (PGL11-024)

#### 14.3.29. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0029

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 5.1 of the SmPC in order to update the safety information with results from study (MO25653) which assessed safety and efficacy of vemurafenib in V600-mutation positive metastatic melanoma patients with previously-treated brain metastases

#### 14.3.30. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0030

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add safety information on acute kidney injury as new adverse drug reaction with a rare frequency. The Package Leaflet and the RMP are updated accordingly

#### 14.3.31. Vemurafenib – ZELBORAF (CAP) - EMEA/H/C/002409/II/0031/G

Applicant: Roche Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC in order to add information on drug-drug interaction of vemurafenib with tizanidine (a CYP1A2 substrate). The RMP (version 10.0) is updated accordingly. In addition, the MAH took the opportunity to update the RMP with a proposed new due date for the final clinical study report of study GO28052 and providing RMP update for the recommendation received during procedure EMEA/H/C/002409/LEG 031 regarding agranulocytosis

## **15. 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 unchanged 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).

### **15.1. PSUR procedures including centrally authorised products only**

#### **15.1.1. Afamelanotide – SCENESSE (CAP) - PSUSA/10314/201506**

---

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Valerie Strassmann

Scope: Evaluation of a PSUSA procedure

#### **15.1.2. Ambrisentan – VOLIBRIS (CAP) - PSUSA/00129/201506**

---

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

#### **15.1.3. Avanafil – SPEDRA (CAP) - PSUSA/10066/201506**

---

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Miguel-Angel Macia

Scope: Evaluation of a PSUSA procedure

#### **15.1.4. Belatacept – NULOJIX (CAP) - PSUSA/00311/201506**

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 15.1.5. Brimonidine tartrate, brinzolamide – SIMBRINZA (CAP) - PSUSA/10273/201506

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### 15.1.6. Bromfenac – YELLOX (CAP) - PSUSA/00436/201505

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of a PSUSA procedure

#### 15.1.7. C1-esterase inhibitor, human – CINRYZE (CAP) - PSUSA/10104/201506

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 15.1.8. Canakinumab – ILARIS (CAP) - PSUSA/00526/201506 (with RMP)

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 15.1.9. Daclatasvir – DAKLINZA (CAP) - PSUSA/10295/201507

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

#### 15.1.10. Dasatinib – SPRYCEL (CAP) - PSUSA/00935/201506

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### 15.1.11. Dextromethorphan hydrobromide, quinidine sulfate – NUEDEXTA (CAP) - PSUSA/10089/201506

Applicant: Jenson Pharmaceutical Services Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 15.1.12. Galsulfase – NAGLAZYME (CAP) - PSUSA/01515/201505

---

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure

#### 15.1.13. Human fibrinogen, human thrombin – EVARREST (CAP), EVICEL (CAP), RAPLIXA (CAP), TACHOSIL (CAP) - PSUSA/10297/201506

---

Applicant: Omrix Biopharmaceuticals N. V., ProFibrix BV, Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 15.1.14. Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP) - PSUSA/01634/201505

---

Applicant: Sanofi Pasteur MSD SNC, Merck Sharp & Dohme Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Evaluation of a PSUSA procedure

#### 15.1.15. Hydroxycarbamide – SIKLOS (CAP) - PSUSA/01692/201506 (with RMP)

---

Applicant: Addmedica

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 15.1.16. Imiglucerase – CEREZYME (CAP) - PSUSA/01727/201505

---

Applicant: Genzyme Europe BV

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### 15.1.17. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - PSUSA/01742/201506

---

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### 15.1.18. Liraglutide – SAXENDA (CAP), VICTOZA (CAP) - PSUSA/01892/201506

---

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

**15.1.19. Matrix applied characterised autologous cultured chondrocytes – MACI (CAP) - PSUSA/10116/201506**

---

Applicant: Aastrom Biosciences DK ApS

PRAC Rapporteur: Rafe Suvarna

Scope: Evaluation of a PSUSA procedure (MA suspension dated 19 November 2014)

**15.1.20. Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches – VELPHORO (CAP) - PSUSA/10296/201505**

---

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**15.1.21. Nepafenac – NEVANAC (CAP) - PSUSA/02143/201505**

---

Applicant: Alcon Laboratories (UK) Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

**15.1.22. Nivolumab – NIVOLUMAB BMS (CAP), OPDIVO (CAP) - PSUSA/10379/201507**

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure (Nivolumab BMS MA withdrawal dated 30 November 2015)

**15.1.23. Nonacog gamma – RIXUBIS (CAP) - PSUSA/10320/201506**

---

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**15.1.24. Olaparib – LYNPARZA (CAP) - PSUSA/10322/201506**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

**15.1.25. Paliperidone – INVEGA (CAP), PALIPERIDONE JANSSEN (CAP), XEPLION (CAP) - PSUSA/02266/201506 (with RMP)**

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue



Scope: Evaluation of a PSUSA procedure

#### **15.1.26. Pegaptanib – MACUGEN (CAP) - PSUSA/02324/201506**

---

Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Jean-Michel Dogné

Scope: Evaluation of a PSUSA procedure

#### **15.1.27. Pegloticase – KRYSTEXXA (CAP) - PSUSA/10046/201507**

---

Applicant: Crealta Pharmaceuticals Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **15.1.28. Pertuzumab – PERJETA (CAP) - PSUSA/10125/201506**

---

Applicant: Roche Registration Limited

PRAC Rapporteur: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### **15.1.29. Secukinumab – COSENTYX (CAP) - PSUSA/10341/201506**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

#### **15.1.30. Sildenafil – REVATIO (CAP) - PSUSA/02700/201505**

---

Applicant: Pfizer Limited

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **15.1.31. Tobramycin – TOBI PODHALER (CAP) - PSUSA/09315/201506**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

## **15.2. PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)**

### **15.2.1. Aminolevulinic acid – AMELUZ (CAP), NAP - PSUSA/10006/201506**

---

Applicant: Biofrontera Bioscience GmbH, various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**15.2.2. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP), NAP - PSUSA/01633/201505**

---

Applicant: Baxalta Innovations GmbH, Baxter AG, CSL Behring GmbH, Instituto Grifols S.A., various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**15.2.3. Imatinib – GLIVEC (CAP), NAP - PSUSA/01725/201505**

---

Applicant: Novartis Europharm Ltd, various

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

**15.2.4. Measles, mumps and rubella vaccine (live) – M-M-RVAXPRO (CAP), NAP - PSUSA/01937/201505**

---

Applicant: Sanofi Pasteur MSD SNC, various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**15.2.5. Nevirapine – VIRAMUNE (CAP), NAP - PSUSA/02147/201505**

---

Applicant: Boehringer Ingelheim International GmbH, various

PRAC Rapporteur: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

**15.2.6. Nitric oxide – INOMAX (CAP), NAP - PSUSA/02172/201506**

---

Applicant: Linde Healthcare AB, various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**15.2.7. Olopatadine – OPATANOL (CAP), NAP - PSUSA/02211/201504**

---

Applicant: Alcon Laboratories (UK) Ltd, various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

### **15.3. PSUR procedures including nationally approved products (NAPs) only**

#### **15.3.1. Ceftriaxone (NAP) - PSUSA/00000613/201505**

---

Applicant: various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### **15.3.2. Cefuroxime sodium (for intracameral use) (NAP) - PSUSA/00010206/201505**

---

Applicant: various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

#### **15.3.3. Clevidipine (NAP) - PSUSA/00010288/201505**

---

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### **15.3.4. Clotiazepam (NAP) - PSUSA/00000827/201505**

---

Applicant: various

PRAC Lead: Veerle Verlinden

Scope: Evaluation of a PSUSA procedure

#### **15.3.5. Diphtheria, tetanus vaccines (adsorbed) (NAP) - PSUSA/00001128/201505**

---

Applicant: various

PRAC Lead: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### **15.3.6. Fentanyl (transdermal patches, solution for injection) (NAP) - PSUSA/00001370/201504**

---

Applicant: various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **15.3.7. Flunarizine (NAP) - PSUSA/00001416/201505**

---

Applicant: various

PRAC Lead: Margarida Guimarães

Scope: Evaluation of a PSUSA procedure

---

**15.3.8. 5 fluorouracil, salicylic acid (NAP) - PSUSA/00000008/201505**

---

Applicant: various

PRAC Lead: Tatiana Magalova

Scope: Evaluation of a PSUSA procedure

---

**15.3.9. Gadoteric acid (intra-articular formulation) (NAP) - PSUSA/00001505/201504**

---

Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

---

**15.3.10. Misoprostol (gynaecological indication, - induction of labour) (NAP) - PSUSA/00010353/201505**

---

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

---

**15.3.11. Misoprostol (gynaecological indication - termination of pregnancy) (NAP) - PSUSA/00010354/201505**

---

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

---

**15.3.12. Nicergoline (NAP) - PSUSA/00002150/201505**

---

Applicant: various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

---

**15.3.13. Pholcodine (NAP) - PSUSA/00002396/201505**

---

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

---

**15.3.14. Praziquantel (NAP) - PSUSA/00002503/201504**

---

Applicant: various

PRAC Lead: Isabelle Robine

Scope: Evaluation of a PSUSA procedure

#### **15.3.15. Ranitidine (NAP) - PSUSA/00002610/201505**

---

Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

#### **15.3.16. Tafluprost (NAP) - PSUSA/00002843/201504**

---

Applicant: various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **15.3.17. Tamoxifen (NAP) - PSUSA/00002846/201504**

---

Applicant: various

PRAC Lead: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### **15.3.18. Terlipressin (NAP) - PSUSA/00002905/201504**

---

Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

#### **15.3.19. Thiamphenicol (NAP) - PSUSA/00002925/201505**

---

Applicant: various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### **15.4. Follow-up to PSUR procedures**

#### **15.4.1. Leflunomide – LEFLUNOMIDE MEDAC (CAP) - EMEA/H/C/001227/LEG 011**

---

Applicant: Medac Gesellschaft fur klinische Spezialpreparate GmbH

PRAC Rapporteur: Sabine Straus

Scope: MAH's review as requested in the conclusions of EMEA/H/C/PSUSA/00001837/201409 adopted by the PRAC in April 2015

#### **15.4.2. Omalizumab – XOLAIR (CAP) - EMEA/H/C/000606/LEG 050**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's review as requested in the conclusions of EMEA/H/C/PSUSA/00002214/201412 adopted by the PRAC in July 2015

#### **15.4.3. Peginterferon beta-1a – PLEGRIDY (CAP) - EMEA/H/C/002827/LEG 007**

---

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's review as requested in the conclusions of EMEA/H/C/PSUSA/00010275/201501 adopted by the PRAC in September 2015

## **16. 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.

### **16.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>43</sup>**

#### **16.1.1. Asfotase alfa - STRENSIQ (CAP) - EMEA/H/C/PSP/0032**

---

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: PASS protocol for study ALX-HPP-501: an observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia to collect information on the epidemiology of the disease, including clinical outcomes and quality of life, and to evaluate safety and effectiveness data in patients treated with Strensiq

#### **16.1.2. Domperidone (NAP) - EMEA/H/N/PSP/j/0016.2**

---

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Isabelle Robine

Scope: Revised joint PASS protocol for a physician survey to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in the product information and the distribution of DHPC

#### **16.1.3. Domperidone (NAP) - EMEA/H/N/PSP/j/0031**

---

Applicant: Janssen (Motilium), various

PRAC Rapporteur: Isabelle Robine

Scope: PASS protocol for a drug utilisation study of domperidone in Europe using databases to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the changes in the product information and the distribution of DHPC. The secondary objective of the study is to

---

<sup>43</sup> In accordance with Article 107n of Directive 2001/83/EC

characterise the extent to which domperidone is prescribed for conditions that are not labelled

#### **16.1.4. Idebenone – RAXONE (CAP) - EMEA/H/C/PSP/0034**

---

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Carmela Macchiarulo

Scope: PASS protocol for a non-interventional study of clinical experience in patients prescribed Raxone for the treatment of Leber's hereditary optic neuropathy (LHON)

#### **16.1.5. Ospemifene – SENSHIO (CAP) - EMEA/H/C/PSP/0023.2**

---

Applicant: Shionogi Limited

PRAC Rapporteur: Julie Williams

Scope: Revised protocol for a PASS to evaluate the incidence of venous thromboembolism and other adverse events, as agreed in the RMP, in vulvar and vaginal atrophy (VVA) patients treated with ospemifene as compared to: 1) patients newly prescribed selective oestrogen receptor modulators (SERMs) for oestrogen-deficiency conditions or breast cancer prevention; 2) the incidence in untreated VVA patients

### **16.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>44</sup>**

#### **16.2.1. Aflibercept – ZALTRAP (CAP) - EMEA/H/C/002532/MEA/002.3**

---

Applicant: Sanofi-Aventis Groupe

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Revised PASS protocol for study OZONE (OBS13597) to reflect Zaltrap usage in clinical practice to address the PRAC request for supplementary information (RSI) adopted in September 2015

#### **16.2.2. Agomelatine – THYMANAX (CAP) - EMEA/H/C/000916/MEA/026.1; VALDOXAN (CAP) - EMEA/H/C/000915/MEA/026.1**

---

Applicant: Servier (Ireland) Industries Ltd., Les Laboratoires Servier

PRAC Rapporteur: Kristin Thorseng Kvande

Scope: MAH's response to MEA 026: revised PASS protocol for study CLE-20098-96-096: non-interventional PASS: DUS in selected European countries: a multinational, observational study to assess the effectiveness of risk-minimisation measures to address the PRAC request for supplementary information (RSI) adopted in October 2015

#### **16.2.3. Bromelain enriched proteolytic enzyme preparation from ananas comosus – NEXOBRID (CAP) - EMEA/H/C/002246/MEA/003.3**

---

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Valerie Strassmann

---

<sup>44</sup> 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: Revised PASS protocol for study MW2013-06-01: drug utilisation study (DUS) to further evaluate the effectiveness of the risk minimisation activities (including evaluation of educational and training materials): MAH's responses to MEA 03.2 request for supplementary information (RSI) as adopted in September 2015

#### 16.2.4. Buprenorphine, naloxone – SUBOXONE (CAP) - EMEA/H/C/000697/MEA/023.5

Applicant: Indivior UK Limited

PRAC Rapporteur: Martin Huber

Scope: Revised protocol for PASS study PE-US-005: suboxone mortality study in the UK with the Health Improvement Network database (THIN): MAH's responses to MEA 023.4 request for supplementary information (RSI) as adopted in September 2015

#### 16.2.5. Cobicistat – TYBOST (CAP) - EMEA/H/C/002572/MEA/012.2

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: MAH's responses to MEA 012.2 request for supplementary information (RSI) as adopted by PRAC in December 2014: request for a waiver for study GS-EU-216-1230: prospective, observational drug utilisation study of cobicistat in adults with human immunodeficiency virus (HIV)-1 infection due to feasibility related issues

#### 16.2.6. Collagenase clostridium histolyticum – XIAPEX (CAP) - EMEA/H/C/002048/MEA/027.1

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Martin Huber

Scope: MAH's responses to MEA 027 [PASS protocol for a non-interventional survey to evaluate the effectiveness of Xiapex educational material for healthcare professionals in the treatment of Peyronie's disease] to address the PRAC request for supplementary information (RSI) as adopted in July 2015

#### 16.2.7. Filgrastim – NIVESTIM (CAP) - EMEA/H/C/001142/MEA/015

Applicant: Hospira UK Limited

PRAC Rapporteur: Kirsti Villikka

Scope: PASS protocol for study ZOB-NIV-1513: a multinational, multicentre, prospective, non-interventional, post-authorisation safety study in healthy donors (HDs) exposed to Nivestim for haematopoietic stem cell (HSC) mobilisation (NEST)

#### 16.2.8. Flutemetamol (<sup>18</sup>F) – VIZAMYL (CAP) - EMEA/H/C/002557/MEA/003.2

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 003.1 request for supplementary information (RSI) adopted by PRAC in September 2015: revised PASS protocol for a drug utilisation study as an additional pharmacovigilance activity to further characterize the safety concern (GE067-028)



#### 16.2.9. Human normal immunoglobulin – PRIVIGEN (CAP) - EMEA/H/C/000831/MEA/022.3

Applicant: CSL Behring GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 022.1 : revised protocol for study IgPro10\_5003 (updated version 2.0): an observational hospital-based cohort study in the US: Privigen use and haemolytic anaemia in adults and children and the Privigen safety profile in children with chronic inflammatory demyelinating polyneuropathy (CIDP)

#### 16.2.10. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/MEA/023.2

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 023.2 [PASS protocol study PCYC-PMR-2060-04] as adopted in September 2015: enhanced pharmacovigilance to evaluate the risks of haemorrhage with the administration of ibrutinib

#### 16.2.11. Meningococcal group b vaccine (rDNA, component, adsorbed) – BEXSERO (CAP) - EMEA/H/C/002333/MEA/017

Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Qun-Ying Yue

Scope: Revised PASS protocol for study V72\_36OB: a post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care

#### 16.2.12. Safinamide – XADAGO (CAP) - EMEA/H/C/002396/MEA/004

Applicant: Zambon SpA

PRAC Rapporteur: Almath Spooner

Scope: Protocol for study Z7219N02, a drug utilisation study (DUS): observational European multicentre retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialisation phase

#### 16.2.13. Sofosbuvir – SOVALDI (CAP) - EMEA/H/C/002798/MEA/021

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Julie Williams

Scope: Protocol for study GS-EU-337-2030: observational, cross-sectional post-authorisation safety study to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)

#### 16.2.14. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/013.1

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: Revised protocol for study GS-EU-337-1820: prospective observational drug utilisation study (DUS) of ledipasvir/sofosbuvir (LDV/SOF) in adults with hepatitis C (HCV)/human immunodeficiency virus (HIV) co-infection

#### **16.2.15. Sofosbuvir, ledipasvir – HARVONI (CAP) - EMEA/H/C/003850/MEA/014**

---

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope: Protocol for study GS-EU-337-2030: observational, cross-sectional PASS to assess healthcare providers awareness of risks related to sofosbuvir and ledipasvir/sofosbuvir (LDV/SOF)

### **16.3. Results of PASS imposed in the marketing authorisation(s)<sup>45</sup>**

None

### **16.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>46</sup>**

- 16.4.1. Abacavir – ZIAGEN (CAP) - EMEA/H/C/000252/WS/0769  
lamivudine – EPIVIR (CAP) - EMEA/H/C/000107/WS/0769, LAMIVUDINE VIIV (Art 58<sup>47</sup>) - EMEA/H/W/000673/WS/0769  
lamivudine, abacavir – KIVEXA (CAP) - EMEA/H/C/000581/WS/0769  
lamivudine, abacavir, zidovudine – TRIZIVIR (CAP) - EMEA/H/C/000338/WS/0769  
lamivudine, zidovudine – COMBIVIR (CAP) - EMEA/H/C/000190/WS/0769 (without RMP)
- 

Applicant: ViiV Healthcare UK Limited

PRAC Rapporteur: Isabelle Robine

Scope: Submission of final clinical study report (CSR) for mitochondrial toxicity in children (MITOC) study (WE027/WWE112888). The MAH took also the opportunity to respond to a LEG on mitochondrial dysfunction to address the request on revision of class labelling of antiretrovirals on mitochondrial toxicity

#### **16.4.2. Catridecacog – NOVOTHIRTEEN (CAP) - EMEA/H/C/002284/II/0012/G**

---

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Isabelle Robine

Scope: Update of the RMP to include exposure and safety data following finalisation of clinical trial F13CD-3835 (evaluation of long term safety of monthly replacement therapy with recombinant factor XIII when used for prevention of bleeding episodes in paediatric subjects with congenital factor XIII A-subunit deficiency). In addition, inclusion of the final study report of PRO-RBDD registry (prospective data collection on congenital factor XIII deficiency)

---

<sup>45</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>46</sup> 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

<sup>47</sup> Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

#### 16.4.3. Eptacog alfa – NOVOSEVEN (CAP) - EMEA/H/C/000074/II/0089 (with RMP)

---

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope: Submission of the final study report NN7025-3601 : prospective observational study on NovoSeven room temperature (VII25) in patients with haemophilia A and B. The submission of this study report addresses MEA 046.4. The RMP (version 6.1) is updated accordingly

#### 16.4.4. Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/II/0073 (with RMP)

---

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report for study 20101120, a category 3 study assessing the impact of the RAS test results on patterns of panitumumab use, intended to measure the effectiveness of the risk minimisation measures for Vectibix. The RMP (version 18.0) is updated accordingly

#### 16.4.5. Telaprevir – INCIVO (CAP) - EMEA/H/C/002313/II/0039

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final results for study VX-950HPC4004: drug utilisation study (DUS) of Incivo (telaprevir) in Europe: adherence to virologic stopping rules and use in patient subgroups as required pharmacovigilance activity (category 3) in the RMP

#### 16.4.6. Vildagliptin – GALVUS (CAP) - EMEA/H/C/000771/WS/0791, JALRA (CAP) - EMEA/H/C/001048/WS/0791, XILIARX (CAP) - EMEA/H/C/001051/WS/0791 Vildagliptin / metformin hydrochloride – EUCREAS (CAP) - EMEA/H/C/000807/WS/0791, ICANDRA (CAP) - EMEA/H/C/001050/WS/0791, ZOMARIST (CAP) - EMEA/H/C/001049/WS/0791 (with RMP)

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final results of PASS study CLAF237A2401 and a revised RMP (version 13.0) to add the study information and to include rhabdomyolysis under the current potential risk as muscle events/myopathy/rhabdomyolysis, in particular with concurrent statin use following the PSUSA/00003113/201502 PRAC recommendation on a signal of rhabdomyolysis with the use of vildagliptin containing products

### 16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>48</sup>

#### 16.5.1. Indacaterol, glycopyrronium bromide – ULTIBRO BREEZHALER (CAP) - EMEA/H/C/002679/MEA/003.3

---

Applicant: Novartis Europharm Ltd

---

<sup>48</sup> In line with the revised variations regulation for any submission before 4 August 2013

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's responses to MEA 003.2 request for supplementary information (RSI) as adopted in October 2015: first interim report for a drug utilisation study CQVA 149A2401

**16.5.2. Indacaterol, glycopyrronium bromide – ULUNAR BREEZHALER (CAP) - EMEA/H/C/003875/MEA/004.2**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's responses to MEA 004.1 request for supplementary information (RSI) as adopted in October 2015: first interim report for a drug utilisation study CQVA 149A2401

**16.5.3. Indacaterol, glycopyrronium bromide – XOTERNA BREEZHALER (CAP) - EMEA/H/C/003755/MEA/003.3**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Torbjorn Callreus

Scope: MAH's responses to MEA 003.2 request for supplementary information (RSI) as adopted in October 2015: first interim report for a drug utilisation study (DUS) CQVA 149A2401

**16.5.4. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA/089.12**

---

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim study reports for the EU rheumatoid arthritis registries: ARTIS and RABBIT cohort 2, ENCORE patient registry in Europe in Crohn's disease

**16.5.5. Infliximab – REMICADE (CAP) - EMEA/H/C/000240/MEA/121.8**

---

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim annual report for study P04808 on the adult ulcerative colitis (UC) patient registry (OPUS), including the investigation of episodic/re-treatment

**16.5.6. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/004.4**

---

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Interim results of the enhanced safety surveillance study D2560C00008: a postmarketing non-interventional cohort study of the safety of live attenuated influenza vaccine (LAIV) in subjects 2 through 17 years of age

**16.5.7. Influenza vaccine (live attenuated, nasal) – FLUENZ TETRA (CAP) - EMEA/H/C/002617/MEA/006.3**

---

Applicant: MedImmune LLC

PRAC Rapporteur: Jean-Michel Dogné

Scope: Second annual report for study MI-MA194: a post-marketing observational evaluation of the safety of Fluenz Tetra in children and adolescents with high-risk conditions

**16.5.8. Influenza vaccine (split virion, inactivated) – IDFLU (CAP) - EMEA/H/C/000966/MEA/032.2; INTANZA (CAP) - EMEA/H/C/000957/MEA/032.2**

---

Applicant: Sanofi Pasteur (IDflu), Sanofi Pasteur MSD SNC (Intanza)

PRAC Rapporteur: Miguel-Angel Macia

Scope: Interim results of the enhanced passive safety surveillance for 2015-2016 campaign

**16.5.9. Nomegestrol, estradiol – ZOELY (CAP) - EMEA/H/C/001213/ANX/011.1**

---

Applicant: Teva B.V.

PRAC Rapporteur: Corinne Fechant

Scope: PASS interim results for a prospective observational study (ZEG2013\_08) to assess the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) in nomegestrol / 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)

**16.5.10. Temsirolimus – TORISEL (CAP) - EMEA/H/C/000799/LEG/031.3**

---

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Interim results from Japanese non-interventional studies 3066K5-4406 (Torisel 25 mg for intravenous drip infusion special investigation - all patients survey) and B1771016 (Torisel 25 mg for intravenous drip infusion special investigation - survey on long term use)

**16.5.11. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/256.5**

---

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: MAH's responses to MEA 256.4 request for supplementary information (RSI) as adopted in September 2015: interim results for a drug utilisation study (DUS), study GS-EU-174-0224 in human immunodeficiency virus (HIV)-1 and hepatitis B virus (HBV)-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures

**16.5.12. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/MEA/272**

---

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Interim report for study GS-DE-174-0225: prospective assessment of the real-life treatment outcomes of six years of Viread in chronic hepatitis B (CHB) following-up on the German multicentre non-interventional study (GEMINIS): VIR-Life

## **16.6. Others**

### **16.6.1. Rivastigmine – EXELON (CAP) - EMEA/H/C/000169/MEA 036.1, PROMETAX (CAP) - EMEA/H/C/000255/MEA 037.1**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Fourth 6-monthly interim report on the trends of multiple patch use and with Council for International Organizations of Medical Sciences (CIOMS) reports of medication errors and misuse (01 February-2015 to 31 July2015)

## **17. 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.

### **17.1. Annual reassessments of the marketing authorisation**

#### **17.1.1. Mecasermin – INCRELEX (CAP) - EMEA/H/C/000704/S/0035 (without RMP)**

---

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

#### **17.1.2. Tafamidis – VYNDAREL (CAP) - EMEA/H/C/002294/S/0031 (without RMP)**

---

Applicant: Pfizer Limited

PRAC Rapporteur: Isabelle Robine

Scope: Annual reassessment of the marketing authorisation

### **17.2. Conditional renewals of the marketing authorisation**

#### **17.2.1. Ceritinib – ZYKADIA (CAP) - EMEA/H/C/003819/R/0004 (without RMP)**

---

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

#### 17.2.2. Delamanid – DELTYBA (CAP) - EMEA/H/C/002552/R/0010 (without RMP)

Applicant: Otsuka Novel Products GmbH

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

#### 17.2.3. Pixantrone dimaleate – PIXUVRI (CAP) - EMEA/H/C/002055/R/0025 (with RMP)

Applicant: CTI Life Sciences Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Conditional renewal of the marketing authorisation

### **17.3. Renewals of the marketing authorisation**

#### 17.3.1. C1 esterase inhibitor, human – CINRYZE (CAP) - EMEA/H/C/001207/R/0040 (without RMP)

Applicant: Shire Services BVBA

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: 5-year renewal of the marketing authorisation

#### 17.3.2. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/R/0042 (with RMP)

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

#### 17.3.3. Ipilimumab – YERVOY (CAP) - EMEA/H/C/002213/R/0035 (with RMP)

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Sabine Straus

Scope: 5-year renewal of the marketing authorisation

#### 17.3.4. Linagliptin – TRAJENTA (CAP) - EMEA/H/C/002110/R/0021 (without RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

## **18. Annex II – List of participants**

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the for the 11-14 January 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
June Munro Raine	Chair	United Kingdom	No interests declared	Full involvement
Marianne Lunzer	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Marina Dimov Di Giusti	Member	Croatia	No interests declared	Full involvement
Nectaroula Cooper	Member	Cyprus	No interests declared	Full involvement
Jana Mladá	Member	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Torbjörn Callreus	Alternate	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Isabelle Robine	Member	France	No interests declared	Full involvement
Corinne Fechant	Alternate	France	No participation in discussions, final deliberations and voting	Human fibrinogen, human thrombin
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests	Full



Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Zane Stade	Alternate	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Kristin Thorseng Kvande	Alternate	Norway	No interests declared	Full involvement
Magdalena Budny	Alternate	Poland	No interests declared	Full involvement
Margarida Guimarães	Member	Portugal	No interests declared	Full involvement
Leonor Chambel	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Tatiana Magálová	Member	Slovakia	No interests declared	Full involvement
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		scientific expert	declared	involvement
Marie Louise (Marieke) De Bruin	Member	Independent scientific expert	No interests declared	Full involvement
Stephen J. W. Evans	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Brigitte Keller-Stanislawski	Member	Independent scientific expert	No interests declared	Full involvement
Herve Le Louet	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Lennart Waldenlind	Member	Independent scientific expert	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Laurence de Fays	Expert - in person*	Belgium	No interests declared	Full involvement
Martin Erik Nyeland - PRAC/SAWP alternate	Expert - in person*	Denmark	No restrictions applicable to this meeting	Full involvement
Serge Bakchine - SAG Chair	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Cécile Francois	Expert - via telephone*	France	No interests declared	Full involvement
Marie-Caroline Pesquidous	Expert - via telephone*	France	No interests declared	Full involvement
Jan Mueller Berghaus	Expert - in person*	Germany	No interests declared	Full involvement
Tobias Lamkemeyer	Expert - via	Germany	No interests	Full

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
	telephone*		declared	involvement
Susanne Winterscheid	Expert - in person*	Germany	No interests declared	Full involvement
Eleanor Carey	Expert - in person*	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Expert - in person*	Ireland	No restrictions applicable to this meeting	Full involvement
Florianne Bauer	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Florence van Hunsel	Expert - in person*	Netherlands	No restrictions applicable to this meeting	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Filip Josephson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Ulf Olsson	Expert - via telephone*	Sweden	No restrictions applicable to this meeting	Full involvement
Patrick Batty	Expert - in person*	United Kingdom	No interests declared	Full involvement
Ana Fernandez Duenas	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jennifer Matthissen	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.

## 19. 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](#)

## 20. 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=W0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=W0b01ac05800240d0)

## **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

## **Risk Management Plans (RMPs)**

(Item 5 of the PRAC minutes)

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

## **Assessment of Periodic Safety Update Reports (PSURs)**

(Item 6 of the PRAC minutes)

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

## **Post-authorisation Safety Studies (PASS)**

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website: [www.ema.europa.eu/](http://www.ema.europa.eu/)