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SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

## Pharmacovigilance Risk Assessment Committee (PRAC) PRAC Minutes of the meeting on 03-06 November 2015

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>11</b>
1.1.	Welcome and declarations of interest of members, alternates and experts.....	11
1.2.	Adoption of agenda of the meeting of 03-06 November 2015.....	11
1.3.	Adoption of the minutes of the previous meeting of 05-08 October 2015.....	11
<b>2.</b>	<b>EU referral procedures for safety reasons: urgent EU procedures</b>	<b>11</b>
2.1.	Newly triggered procedures .....	11
2.2.	Ongoing procedures .....	11
2.3.	Procedures for finalisation.....	12
2.4.	Planned public hearings.....	12
<b>3.</b>	<b>EU referral procedures for safety reasons: other EU referral procedures</b>	<b>12</b>
3.1.	Newly triggered procedures .....	12
3.2.	Ongoing procedures .....	12
3.2.1.	Inhaled corticosteroids (ICS)-containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease: beclomethasone (NAP); beclomethasone, formoterol (NAP); budesonide (NAP); budesonide, formoterol – BIRESP SPIROMAX (CAP); BUDESONIDE FORMOTEROL TEVA (CAP); DUORESP SPIROMAX (CAP); VYALER SPIROMAX (CAP); flunisolide, salbutamol (NAP); fluticasone (NAP); fluticasone, salmeterol (NAP); fluticasone, vilanterol – RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) – EMEA/H/A-31/1415 .....	12
3.2.2.	Natalizumab – TYSABRI (CAP) - EMEA/H/A-20/1416 .....	12
3.3.	Procedures for finalisation.....	13
3.3.1.	Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP) Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) – GARDASIL 9 (CAP) - EMEA/H/A-20/1421 .....	13
3.4.	Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request .....	14
3.5.	Others .....	14
<b>4.</b>	<b>Signals assessment and prioritisation</b>	<b>14</b>
4.1.	New signals detected from EU spontaneous reporting systems .....	14
4.1.1.	Axitinib – INLYTA (CAP).....	14
4.1.2.	Bevacizumab – AVASTIN (CAP) .....	15
4.1.3.	Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP), NAP .....	16
4.1.4.	Mercaptopurine - XALUPRINE (CAP); NAP .....	17
4.1.5.	Somatropin - NUTROPINAQ (CAP), OMNITROPE (CAP), SOMATROPIN BIOPARTNERS (CAP), NAP .....	18
4.1.6.	Tigecycline – TYGACIL (CAP).....	19

<b>4.2.</b>	<b>New signals detected from other sources .....</b>	<b>20</b>
4.2.1.	Methotrexate - NAP.....	20
4.2.2.	Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP) .....	21
4.2.3.	Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); duloxetine (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP); venlafaxine (NAP) .....	22
<b>4.3.</b>	<b>Signals follow-up and prioritisation .....</b>	<b>24</b>
4.3.1.	Aflibercept - EYLEA (CAP) – EMEA/H/C/002392/SDA/012.....	24
4.3.2.	Human fibrinogen, human thrombin – TACHOSIL (CAP) - EMEA/H/C/000505/SDA/041 ....	25
4.3.3.	Oxybutynin – KENTERA (CAP) - EMEA/H/C/000532/SDA/021 .....	25
4.3.4.	Palifermin – KEPIVANCE (CAP) - EMEA/H/C/000609/SDA/054 .....	26
4.3.5.	Warfarin (NAP) .....	27
<b>5.</b>	<b>Risk management plans (RMPs) .....</b>	<b>28</b>
<b>5.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>28</b>
5.1.1.	Albutrepenonacog alfa - EMEA/H/C/003955, Orphan .....	28
5.1.2.	Eptifibatide - EMEA/H/C/004104 .....	28
5.1.3.	Factor X - EMEA/H/C/003855, Orphan.....	28
5.1.4.	Grazoprevir, elbasvir - EMEA/H/C/004126 .....	28
<b>5.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures.....</b>	<b>29</b>
5.2.1.	Orlistat – ALLI (CAP) - EMEA/H/C/000854/II/0052.....	29
5.2.2.	Sevelamer – RENAGEL (CAP) - EMEA/H/C/000254/WS/0803; RENVELA (CAP) - EMEA/H/C/000993/WS/0803; SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS/0803; TASERMITY (CAP) - EMEA/H/C/003968/WS/0803.....	29
<b>5.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures .....</b>	<b>30</b>
5.3.1.	Deferasirox – EXJADE (CAP) - EMEA/H/C/000670/X/0043.....	30
5.3.2.	Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0184 .....	31
5.3.3.	Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0077 .....	32
<b>6.</b>	<b>Periodic safety update reports (PSURs) .....</b>	<b>33</b>
<b>6.1.</b>	<b>PSUR procedures including centrally authorised products (CAPs) only .....</b>	<b>33</b>
6.1.1.	Bortezomib – VELCADE (CAP) - PSUSA/00424/201504 .....	33
6.1.2.	Ceftaroline fosamil – ZINFORO (CAP) - PSUSA/10013/201504 .....	34
6.1.3.	Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - PSUSA/01745/201504 .....	35
6.1.4.	Lurasidone – LATUDA (CAP) - PSUSA/10114/201504 .....	35
6.1.5.	Mannitol – BRONCHITOL (CAP) - PSUSA/09226/201504 .....	36
6.1.6.	Nintedanib – OFEV (CAP) - PSUSA/10319/201504 .....	37
6.1.7.	Sunitinib – SUTENT (CAP) - PSUSA/02833/201504 .....	38
6.1.8.	Temsirolimus – TORISEL (CAP) - PSUSA/02887/201503 .....	39
6.1.9.	Thiotepa – TEPADINA (CAP) - PSUSA/02932/201503 .....	39

6.1.10.	Vandetanib – CAPRELSA (CAP) - PSUSA/09327/201504 .....	40
<b>6.2.</b>	<b>PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>41</b>
6.2.1.	Bimatoprost – LUMIGAN (CAP), NAP - PSUSA/00413/201503 .....	41
<b>6.3.</b>	<b>PSUR procedures including nationally authorised products (NAPs) only .....</b>	<b>42</b>
6.3.1.	Cabergoline (NAP) - PSUSA/00477/201503.....	42
6.3.2.	Calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, sodium hydroxide (NAP) - PSUSA/09162/201503 .....	43
6.3.3.	Spirolactone (NAP) - PSUSA/02780/201503 .....	44
6.3.4.	Trandolapril, verapamil (NAP) - PSUSA/03005/201503 .....	45
<b>6.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>45</b>
6.4.1.	Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBP), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – INFANRIX HEXA (CAP) - EMEA/H/C/000296/LEG 116 .....	45
<b>7.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>46</b>
<b>7.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>46</b>
7.1.1.	Deferasirox – EXJADE (CAP) - EMEA/H/C/PSP/0010.4.A.1.....	46
7.1.2.	Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/0024.1 .....	47
<b>7.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>47</b>
7.2.1.	Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/MEA/011.1 .....	47
<b>7.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s).....</b>	<b>48</b>
<b>7.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s).....</b>	<b>48</b>
<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>48</b>
<b>7.6.</b>	<b>Others .....</b>	<b>48</b>
<b>7.7.</b>	<b>New Scientific Advice .....</b>	<b>49</b>
<b>8.</b>	<b>Renewals of the marketing authorisation, conditional renewal and annual reassessments .....</b>	<b>49</b>
<b>8.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>49</b>
<b>8.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>49</b>
<b>8.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>49</b>
8.3.1.	Apixaban – ELIQUIS (CAP) - EMEA/H/C/0002148/R/0034 (with RMP).....	49
8.3.2.	Retigabine – TROBALT (CAP) - EMEA/H/C/001245/R/0036 (with RMP) .....	50
<b>9.</b>	<b>Product related pharmacovigilance inspections .....</b>	<b>50</b>
<b>9.1.</b>	<b>List of planned pharmacovigilance inspections.....</b>	<b>51</b>
<b>9.2.</b>	<b>Ongoing or concluded pharmacovigilance inspections.....</b>	<b>51</b>
<b>10.</b>	<b>Other safety issues for discussion requested by the CHMP or the EMA .....</b>	<b>51</b>
<b>10.1.</b>	<b>Safety related variations of the marketing authorisation.....</b>	<b>51</b>

<b>10.2.</b>	<b>Timing and message content in relation to Member States' safety announcements</b>	<b>51</b>
<b>10.3.</b>	<b>Other requests</b>	<b>51</b>
<b>11.</b>	<b>Other safety issues for discussion requested by the Member States</b>	<b>51</b>
<b>11.1.</b>	<b>Safety related variations of the marketing authorisation</b>	<b>51</b>
<b>11.2.</b>	<b>Other requests</b>	<b>51</b>
<b>12.</b>	<b>Organisational, regulatory and methodological matters</b>	<b>51</b>
<b>12.1.</b>	<b>Mandate and organisation of the PRAC</b>	<b>51</b>
12.1.1.	Using PRAC plenary time efficiently and effectively – follow-up from discussion at the Luxembourg PRAC strategic review and learning meeting	51
<b>12.2.</b>	<b>Coordination with EMA Scientific Committees or CMDh</b>	<b>52</b>
12.2.1.	CHMP guideline concerning tools for early access to medicines - accelerated assessment - revision	52
12.2.2.	CHMP guideline concerning tools for early access to medicines - conditional marketing authorisation - revision	52
12.2.3.	Joint Paediatric Committee (PDCO)-PRAC Working Group - guideline on conduct of pharmacovigilance for medicines used by the paediatric population	52
12.2.4.	Paediatric pharmacovigilance - organ maturation tables	52
<b>12.3.</b>	<b>Coordination with EMA Working Parties/Working Groups/Drafting Groups</b>	<b>52</b>
12.3.1.	EMA workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants (DOAC) on 23 November 2015	52
12.3.2.	Scientific Advice Working Party (SAWP) – update on pilot for non-imposed PASS protocols	53
12.3.3.	Working Party with Healthcare Professionals' Organisations (HCPWP)- work plan 2016	53
12.3.4.	Working Party with Patients' and Consumers' Organisations (PCWP) – work plan 2016	53
<b>12.4.</b>	<b>Cooperation within the EU regulatory network</b>	<b>53</b>
<b>12.5.</b>	<b>Cooperation with International Regulators</b>	<b>53</b>
<b>12.6.</b>	<b>Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee</b>	<b>53</b>
<b>12.7.</b>	<b>PRAC work plan</b>	<b>54</b>
12.7.1.	PRAC work plan 2016 - development	54
<b>12.8.</b>	<b>Planning and reporting</b>	<b>54</b>
<b>12.9.</b>	<b>Pharmacovigilance audits and inspections</b>	<b>54</b>
12.9.1.	Pharmacovigilance systems and their quality systems	54
12.9.2.	Pharmacovigilance inspections	54
12.9.3.	Pharmacovigilance audits	54
<b>12.10.</b>	<b>Periodic safety update reports (PSURs) &amp; Union reference date (EURD) list</b>	<b>54</b>
12.10.1.	Granularity and Periodicity Advisory Group (GPAG)	54
12.10.2.	Periodic Safety Update Reports Single Assessment (PSUSA) – proactive publication of PRAC assessment reports for nationally approved products (NAPs)	54
12.10.3.	PSURs repository	54

12.10.4.	Union reference date list – consultation on the draft list .....	55
<b>12.11.</b>	<b>Signal management .....</b>	<b>55</b>
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group .....	55
<b>12.12.</b>	<b>Adverse drug reactions reporting and additional reporting .....</b>	<b>55</b>
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	55
12.12.2.	Additional monitoring .....	55
12.12.3.	List of products under additional monitoring – consultation on the draft list .....	56
<b>12.13.</b>	<b>EudraVigilance database.....</b>	<b>56</b>
12.13.1.	Activities related to the confirmation of full functionality - EudraVigilance auditable requirement communication plan.....	56
12.13.2.	EudraVigilance Access Policy – technical implementation .....	56
<b>12.14.</b>	<b>Risk management plans and effectiveness of risk minimisations.....</b>	<b>56</b>
12.14.1.	Risk management systems .....	56
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations .....	56
<b>12.15.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>56</b>
12.15.1.	Post-authorisation Safety Studies – imposed PASS .....	56
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS .....	56
<b>12.16.</b>	<b>Community procedures.....</b>	<b>57</b>
12.16.1.	Referral procedures for safety reasons .....	57
<b>12.17.</b>	<b>Renewals, conditional renewals, annual reassessments.....</b>	<b>57</b>
12.17.1.	Conditional renewals and annual re-assessments - revision of assessment report templates .....	57
<b>12.18.</b>	<b>Risk communication and transparency .....</b>	<b>57</b>
12.18.1.	Public participation in pharmacovigilance.....	57
12.18.2.	Safety communication - PRAC meeting highlights .....	57
<b>12.19.</b>	<b>Continuous pharmacovigilance .....</b>	<b>57</b>
12.19.1.	Rapid Alert/Non-Urgent Information (RA/NUI) – templates update.....	57
<b>12.20.</b>	<b>Others .....</b>	<b>58</b>
<b>13.</b>	<b>Any other business .....</b>	<b>58</b>
<b>13.1.</b>	<b>Strategy on impact of pharmacovigilance.....</b>	<b>58</b>
<b>14.</b>	<b>Annex I – Risk management plans .....</b>	<b>59</b>
<b>14.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>59</b>
14.1.1.	Amlodipine, valsartan - EMEA/H/C/004037 .....	59
14.1.2.	Betulae cortex dry extract - EMEA/H/C/003938 .....	59
14.1.3.	Brivaracetam - EMEA/H/C/003898 .....	59
14.1.4.	Elotuzumab - EMEA/H/C/003967, Orphan.....	59
14.1.5.	Etanercept - EMEA/H/C/004007.....	59
14.1.6.	Ferric maltol - EMEA/H/C/002733 .....	59

14.1.7.	Mercaptamine - EMEA/H/C/004038, Orphan.....	59
14.1.8.	Mercaptamine - EMEA/H/C/003769, Orphan.....	59
14.1.9.	Necitumumab - EMEA/H/C/003886 .....	60
14.1.10.	Opicapone - EMEA/H/C/002790 .....	60
14.1.11.	Pegaspargase - EMEA/H/C/003789 .....	60
14.1.12.	Pemetrexed - EMEA/H/C/004072 .....	60
14.1.13.	Pitolisant - EMEA/H/C/002616, Orphan.....	60
14.1.14.	Recombinant L-asparaginase - EMEA/H/C/002661, Orphan .....	60
<b>14.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedure .....</b>	<b>60</b>
14.2.1.	Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/II/0154/G .....	60
14.2.2.	Zoledronic acid – ACLASTA (CAP) - EMEA/H/C/000595/II/0056 .....	60
14.2.3.	Zoledronic acid – ZOMETA (CAP) - EMEA/H/C/000336/II/0069 .....	61
<b>14.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedure.....</b>	<b>61</b>
14.3.1.	Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0039.....	61
14.3.2.	Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0062 .....	61
14.3.3.	Bromfenac – YELLOX (CAP) - EMEA/H/C/000098/R/0014.....	61
14.3.4.	Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0010/G .....	61
14.3.5.	Denosumab – XGEVA (CAP) - EMEA/H/C/002173/II/0041 .....	62
14.3.6.	Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP) - EMEA/H/C/002702/WS/0789; HEXAXIM (Art 58) - EMEA/H/W/002495/WS/0789; HEXYON (CAP) - EMEA/H/C/002796/WS/0789 .....	62
14.3.7.	Eltrombopag – REVOLADE (CAP) - EMEA/H/C/001110/X/0022/G .....	62
14.3.8.	Eribulin – HALAVEN (CAP) - EMEA/H/C/002084/II/0028 .....	62
14.3.9.	Eslicarbazepine acetate – ZEBINIX (CAP) - EMEA/H/C/000988/X/0050/G .....	63
14.3.10.	Everolimus – AFINITOR (CAP) - EMEA/H/C/001038/II/0048 .....	63
14.3.11.	Everolimus – VOTUBIA (CAP) - EMEA/H/C/002311/II/0039.....	63
14.3.12.	Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0065/G .....	63
14.3.13.	Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0063 .....	63
14.3.14.	Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP) - EMEA/H/C/002493/II/0017/G .....	64
14.3.15.	Human fibrinogen, human thrombin – EVICEL (CAP) - EMEA/H/C/000898/II/0032.....	64
14.3.16.	Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067 .....	64
14.3.17.	Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/II/0078 .....	64
14.3.18.	Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0013.....	64
14.3.19.	Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/II/0006.....	65
14.3.20.	Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0056 .....	65
14.3.21.	Nivolumab – NIVOLUMAB BMS (CAP) - EMEA/H/C/003840/II/0001 .....	65



14.3.22.	Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0001/G .....	65
14.3.23.	Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0002 .....	65
14.3.24.	Peramppanel – FYCOMPA (CAP) - EMEA/H/C/002434/II/0023 .....	66
14.3.25.	Pyronaridine – PYRAMAX (Art 58) - EMEA/H/W/002319/II/0002 .....	66
14.3.26.	Pyronaridine – PYRAMAX (Art 58) - EMEA/H/W/002319/X/0008/G .....	66
14.3.27.	Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - EMEA/H/C/000674/R/0096 ..	66
14.3.28.	Teduglutide – REVESTIVE (CAP) - EMEA/H/C/002345/II/0020 .....	66
14.3.29.	Ticagrelor – BRILIQUE (CAP) - EMEA/H/C/001241/X/0029/G .....	67

## **15. ANNEX I - Periodic safety update reports (PSURs) 67**

<b>15.1.</b>	<b>PSUR procedures including centrally authorised products only .....</b>	<b>67</b>
15.1.1.	Abiraterone – ZYTIGA (CAP) - PSUSA/00015/201504.....	67
15.1.2.	Alipogene tiparvovec – GLYBERA (CAP) - PSUSA/10056/201504.....	67
15.1.3.	Alogliptin – VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone – INCRESYNC (CAP) - PSUSA/10061/201504 .....	67
15.1.4.	Bazedoxifene, estrogens conjugated – DUAVIVE (CAP) - PSUSA/10321/201504 .....	67
15.1.5.	Budesonide, formoterol fumarate dihydrate – BIRESP SPIROMAX (CAP), BUDESONIDE/FORMOTEROL TEVA (CAP), BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP), DUORESP SPIROMAX (CAP), VYLAER SPIROMAX (CAP) - PSUSA/10202/201504 ....	68
15.1.6.	Cabozantinib – COMETRIQ (CAP) - PSUSA/10180/201503 .....	68
15.1.7.	Catumaxomab – REMOVAB (CAP) - PSUSA/00581/201504 .....	68
15.1.8.	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP) - PSUSA/00273/201504 .....	68
15.1.9.	Conestat alfa – RUCONEST (CAP) - PSUSA/00873/201504.....	68
15.1.10.	Defibrotide – DEFITELIO (CAP) - PSUSA/10086/201504 .....	68
15.1.11.	Delamanid – DELTYBA (CAP) - PSUSA/10213/201504 .....	68
15.1.12.	Dihydroartemisinin, piperaquine tetraphosphate – EURARTESIM (CAP) - PSUSA/01069/201504.....	69
15.1.13.	Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP), HEXAXIM (Art 58), HEXYON (CAP) - PSUSA/10091/201504 .....	69
15.1.14.	Empagliflozin – JARDIANCE (CAP) - PSUSA/10219/201504 .....	69
15.1.15.	Febuxostat – ADENURIC (CAP) - PSUSA/01353/201504 .....	69
15.1.16.	Fenofibrate, pravastatin – PRAVAFENIX (CAP) - PSUSA/01363/201504 .....	69
15.1.17.	Florbetapir ( <sup>18</sup> F) – AMYVID (CAP) - PSUSA/10032/201504 .....	69
15.1.18.	Flutemetamol ( <sup>18</sup> F) – VIZAMYL (CAP) - PSUSA/10293/201504.....	70
15.1.19.	Granisetron – SANCUSO (CAP) - PSUSA/10101/201504 .....	70
15.1.20.	Histamine – CEPLENE (CAP) - PSUSA/01610/201504 .....	70
15.1.21.	Ibrutinib – IMBRUVICA (CAP) - PSUSA/10301/201504 .....	70
15.1.22.	Influenza vaccine (split virion, inactivated) – IDFLU (CAP), INTANZA (CAP) - PSUSA/01743/201504.....	70



15.1.23.	Insulin glulisine – APIDRA (CAP) - PSUSA/01752/201504 .....	70
15.1.24.	Ivabradine – CORLENTOR (CAP), PROCORALAN (CAP) - PSUSA/01799/201504 .....	70
15.1.25.	Laronidase – ALDURAZYME (CAP) - PSUSA/01830/201504 .....	71
15.1.26.	Ledipasvir, sofosbuvir – HARVONI (CAP) - PSUSA/10306/201504 .....	71
15.1.27.	Macitentan – OPSUMIT (CAP) - PSUSA/10115/201504 .....	71
15.1.28.	Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - PSUSA/10044/201504.....	71
15.1.29.	Obinutuzumab – GAZYVARO (CAP) - PSUSA/10279/201504.....	71
15.1.30.	Ocriplasmin – JETREA (CAP) - PSUSA/10122/201504.....	71
15.1.31.	Ofatumumab – ARZERRA (CAP) - PSUSA/02202/201504 .....	71
15.1.32.	Para-aminosalicylic acid – GRANUPAS (CAP) - PSUSA/10171/201504.....	72
15.1.33.	Propranolol – HEMANGIOL (CAP) - PSUSA/10250/201504.....	72
15.1.34.	Ramucirumab – CYRAMZA (CAP) - PSUSA/10323/201504.....	72
15.1.35.	Regadenoson – RAPISCAN (CAP) - PSUSA/02616/201504 .....	72
15.1.36.	Siltuximab – SYLVANT (CAP) - PSUSA/10254/201504 .....	72
15.1.37.	Tocilizumab – ROACTEMRA (CAP) - PSUSA/02980/201504.....	72
15.1.38.	Turoctocog alfa – NOVOEIGHT (CAP) - PSUSA/10138/201504 .....	72
15.1.39.	Umeclidinium bromide – INCRUSE (CAP) - PSUSA/10263/201504.....	73
15.1.40.	Yttrium ( <sup>90</sup> Y) chloride – YTRACIS (CAP), YTRIGA (CAP) - PSUSA/03137/201503 .....	73
<b>15.2.</b>	<b>PSUR procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>73</b>
15.2.1.	Telmisartan - MICARDIS (CAP), KINZALMONO (CAP), PRITOR (CAP), NAP hydrochlorothiazide, telmisartan – KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP) - PSUSA/02882/201504 .....	73
15.2.2.	Tenofovir – VIREAD (CAP), NAP - PSUSA/02892/201503 .....	73
<b>15.3.</b>	<b>PSUR procedures including nationally approved products (NAPs) only .....</b>	<b>73</b>
15.3.1.	Dobutamine (NAP) - PSUSA/01151/201503 .....	73
15.3.2.	Latanoprost (paediatric indication) (NAP) - PSUSA/01834/201504 .....	73
15.3.3.	Nitrazepam (NAP) - PSUSA/02170/201503 .....	74
15.3.4.	Pimecrolimus (NAP) - PSUSA/02411/201503.....	74
15.3.5.	Triamcinolone (intraocular formulations) (NAP) - PSUSA/10292/201503.....	74
<b>16.</b>	<b>ANNEX I – Post-authorisation safety studies (PASS) .....</b>	<b>74</b>
<b>16.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>74</b>
16.1.1.	Tolvaptan – JINARC (CAP) - EMEA/H/C/PSP/0028.1 .....	74
<b>16.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>74</b>
16.2.1.	Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/MEA/005.....	74
16.2.2.	Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/MEA/025.2; LIPROLOG (CAP) - EMEA/H/C/000393/MEA/018.2 .....	75
16.2.3.	Interferon beta-1a – AVONEX (CAP) - EMEA/H/C/000102/MEA/084.3.....	75
16.2.4.	Interferon beta-1a – REBIF (CAP) - EMEA/H/C/000136/MEA/039.3 .....	75

16.2.5.	Interferon beta-1b – BETA FERON (CAP) - EMEA/H/C/000081/MEA/021.3 .....	75
16.2.6.	Interferon beta-1b – EXTAVIA (CAP) - EMEA/H/C/000933/MEA/019.3 .....	75
16.2.7.	Linacotide – CONSTELLA (CAP) - EMEA/H/C/002490/MEA/009.2 .....	76
16.2.8.	Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/002.1 .....	76
16.2.9.	Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/004.1 .....	76
16.2.10.	Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/006.1 .....	76
16.2.11.	Naltrexone, bupropion – MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003 .....	76
16.2.12.	Naltrexone, bupropion – MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004 .....	76
16.2.13.	Nivolumab – NIVOLUMAB BMS (CAP) - EMEA/H/C/003840/MEA/007; OPDIVO (CAP) - EMEA/H/C/003985/MEA/008 .....	77
<b>16.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s) .....</b>	<b>77</b>
<b>16.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>77</b>
16.4.1.	Dexmedetomidine – DEXDOR (CAP) - EMEA/H/C/002268/II/0014 (without RMP) .....	77
16.4.2.	Fondaparinux sodium – ARIXTRA (CAP) - EMEA/H/C/000403/II/0067 (with RMP) .....	77
16.4.3.	Memantine – AXURA (CAP) - EMEA/H/C/000378/WS/0804; EBIXA (CAP) - EMEA/H/C/000463/WS/0804; MEMANTINE MERZ (CAP) - EMEA/H/C/002711/WS/0804 (with RMP) .....	77
16.4.4.	Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/II/0071 (with RMP) .....	78
16.4.5.	Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS0731/0147 (with RMP) tenofovir disoproxil, emtricitabine – EVIPLERA (CAP) - EMEA/H/C/002312/WS0731/0056; TRUVADA (CAP) - EMEA/H/C/000594/WS0731/0113 - (with RMP) tenofovir disoproxil, emtricitabine, efavirenz – ATRIPLA (CAP) - EMEA/H/C/000797/WS0731/0101 (with RMP) tenofovir disoproxil, emtricitabine, elvitegravir, cobicistat – STRIBILD (CAP) - EMEA/H/C/002574/WS0731/0044 (with RMP) .....	78
<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>78</b>
16.5.1.	Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.5 .....	78
16.5.2.	Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.4 .....	78
<b>17.</b>	<b>Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments .....</b>	<b>79</b>
<b>17.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>79</b>
17.1.1.	Anagrelide – XAGRID (CAP) - EMEA/H/C/000480/S/0064 (without RMP) .....	79
17.1.2.	Canakinumab – ILARIS (CAP) - EMEA/H/C/0001109/S/0042 (without RMP) .....	79
<b>17.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>79</b>
17.2.1.	Bedaquiline – SIRTURO (CAP) - EMEA/H/C/0002614/R/0010 (without RMP) .....	79
17.2.2.	Bosutinib – BOSULIF (CAP) - EMEA/H/C/002373/R/0019 (without RMP) .....	79
17.2.3.	Cabozantinib – COMETRIQ (CAP) - EMEA/H/C/002640/R/0017 (without RMP) .....	79
<b>18.</b>	<b>Annex II – List of participants .....</b>	<b>80</b>
<b>19.</b>	<b>Annex III - List of acronyms and abbreviations .....</b>	<b>84</b>
<b>20.</b>	<b>Explanatory notes .....</b>	<b>84</b>

## 1. Introduction

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

The Chair opened the 3-6 November 2015 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 Neikena as the new member for Latvia, moving from her position as alternate.

### 1.2. Adoption of agenda of the meeting of 03-06 November 2015

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

### 1.3. Adoption of the minutes of the previous meeting of 05-08 October 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 5-8 October 2015 were published on the EMA website on 27 November 2015 ([EMA/PRAC/725044/2015](#)).

## 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. Inhaled corticosteroids (ICS)-containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease: beclomethasone (NAP); beclomethasone, formoterol (NAP); budesonide (NAP); budesonide, formoterol – BIRESP SPIROMAX (CAP); BUDESONIDE FORMOTEROL TEVA (CAP); DUORESP SPIROMAX (CAP); VYALER SPIROMAX (CAP); fluticasone, salbutamol (NAP); fluticasone (NAP); fluticasone, salmeterol (NAP); fluticasone, vilanterol – RELVAR ELLIPTA (CAP); REVINTY ELLIPTA (CAP) – EMEA/H/A-31/1415

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Applicant: Glaxo Group Ltd, Teva Pharma B.V., Teva Pharmaceuticals Europe, various  
PRAC Rapporteur: Rafe Suvarna; PRAC Co-rapporteur: Jan Neuhauser

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing to review all available data for inhaled corticosteroids (ICS)-containing products indicated in the treatment of chronic obstructive pulmonary disease (COPD) in order to further characterise the risk of pneumonia and to assess whether the product information appropriately reflects this risk. For background information, see [PRAC minutes May 2015](#).

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

The PRAC discussed the conclusion reached by the Rapporteurs and agreed on a list of outstanding issues (LoOI), to be addressed by the MAH in accordance with a revised timetable ([EMA/PRAC/290163/2015 rev. 2](#)).

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

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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](#) and [PRAC minutes October 2015](#).

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

The PRAC endorsed the list of experts for the Scientific Advisory Group on Neurology (SAG-N) scheduled on 6 November 2015.

## **3.3. Procedures for finalisation**

- 3.3.1. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP)  
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed) – GARDASIL (CAP), SILGARD (CAP)  
Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed) – GARDASIL 9 (CAP) - EMEA/H/A-20/1421
- 

Applicant: GlaxoSmithKline Biologicals S.A. (Cervarix), Sanofi Pasteur MSD SNC (Gardasil, Gardasil 9), Merck Sharp & Dohme Limited (Silgard)

PRAC Rapporteur: Julie Williams; PRAC Co-rapporteurs: Jean-Michel Dogné, Qun-Ying Yue

Scope: Review to further clarify the safety profile of human papillomavirus vaccines following notification by the European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

### **Background**

A referral procedure under Article 20 of Regulation (EC) No 726/2004 to further clarify the safety profile of Cervarix, Gardasil, Gardasil 9 and Silgard (human papillomavirus vaccines) in relation to the available data regarding complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) is to be concluded. An updated assessment of the submitted data was produced by the Rapporteurs according to the agreed timetable. For more background information, see [PRAC minutes July 2015](#), [PRAC minutes September 2015](#) and [PRAC minutes October 2015](#).

### **Discussion**

The PRAC considered the totality of the data submitted with regard to a potential association between HPV vaccines and the occurrence of CRPS and POTS. This included the responses submitted by the MAHs, published literature, EudraVigilance data, the outcome of the Scientific Advisory Group-Vaccines (SAG-V) held on 21 October 2015, data submitted by Member States and the public. The PRAC took note of the fact that CRPS and POTS occur in the general unvaccinated population and have been described in the medical literature

before HPV vaccines were introduced. The PRAC considered that the observed versus expected analyses took into account a wide range of scenarios regarding underreporting and included reports that did not fully meet the diagnostic criteria for the syndromes. Overall, in these analyses the rates of these syndromes in vaccinated girls were consistent with expected rates in these age groups. The PRAC also noted that most of the reviewed reports of POTS would more appropriately have been labelled as having features of chronic fatigue syndrome (CFS). Therefore, the PRAC considered the results of a large published study which showed no link between HPV vaccine and CFS, as relevant for the current review.

Taking into account the totality of the available data, the PRAC concluded that the available evidence does not support that HPV vaccines cause CRPS or POTS. Therefore, there is no reason to change the way the vaccines are currently used or amend the current product information. The safety of these vaccines will remain under close review and it was agreed that follow-up of reports of CRPS or POTS should enable determination of relevant clinical characteristics and also should aim to identify possible cases of CRPS and POTS based on broad search strategies.

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

The PRAC adopted, by consensus, the maintenance of the marketing authorisations for Cervarix, Gardasil, Gardasil 9 and Silgard (human papillomavirus vaccines) and adopted a recommendation to be considered by the CHMP for an opinion. See EMA press release ([EMA/714950/2015](#)) entitled 'Review concludes evidence does not support that HPV vaccines cause CRPS or POTS'.

Post-meeting note: the press release entitled 'HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS' ([EMA/749763/2015](#)) representing the opinion adopted by the CHMP was published on the EMA website on 20 November 2015. The PRAC assessment report ([EMA/762033/2015](#)) taken into account by the CHMP in its opinion was published on 26 November 2015.

## **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. Axitinib – INLYTA (CAP)**

Applicant: Pfizer Limited

<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

PRAC Rapporteur: Ingebjorg Buajordet

Scope: Signal of nephrotic syndrome  
EPITT 18484 – New signal  
Lead Member State: NO

### **Background**

Axitinib is a tyrosine kinase inhibitor (TKI) indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) under certain conditions.

The exposure for Inlyta, a centrally authorised medicine containing axitinib, is estimated to have been more than 24,304 patients worldwide, in the period from first authorisation in 2012 until January 2015.

During routine signal detection activities, a signal of nephrotic syndrome was identified by the EMA, based on 11 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 the plausible biological mechanism, and the positive dechallenge observed in several cases, the PRAC agreed to request the MAH to provide a cumulative review of all cases concerning nephrotic syndrome and related terms associated with the use of axitinib.

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

- The MAH for Inlyta (axitinib) should submit to the EMA, within 60 days, a cumulative review of all cases concerning nephrotic syndrome and related terms associated with the use of axitinib. This review should include data from scientific publications, clinical trials and spontaneous case reports with a discussion on the underlying mechanism of nephrotic syndrome. The MAHs should discuss any potential amendment to the product information and/or 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. Bevacizumab – AVASTIN (CAP)**

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Applicant: Roche Registration Ltd

PRAC Rapporteur: Doris Stenver

Scope: Signal of generalised tonic-clonic seizures  
EPITT 18485 – New signal  
Lead Member State: DK

### **Background**

Bevacizumab is a vascular endothelial growth factor (VEGF) receptor inhibitor indicated in combination for the treatment of adult patients with metastatic carcinoma of the colon or rectum, for first-line treatment of adult patients with metastatic breast cancer under certain conditions, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, for first-line treatment of adult patients with advanced and/or metastatic renal



cell cancer, for the first-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian or platinum-resistant recurrent, fallopian tube or primary peritoneal cancer under certain conditions as well as for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

The post-marketing exposure for Avastin, a centrally authorised medicine containing bevacizumab, is estimated to have been more than 2,048,911 patients worldwide, in the period from first authorisation in 2005 until February 2015.

During routine signal detection activities, a signal of generalised tonic-clonic seizures was identified by the EMA, based on 6 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 a causal relationship between bevacizumab and generalised tonic-clonic seizures cannot be excluded, the PRAC agreed to request the MAH to provide a cumulative review of seizures in association with bevacizumab, with a focus on generalized tonic-clonic seizures.

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

- The MAH for Avastin (bevacizumab) should submit to the EMA, in the next PSUR (DLP: 25/02/2016) (PSUSA/00000403/201602) a cumulative review of seizures in association with bevacizumab, with a focus on generalized tonic-clonic seizures.

#### **4.1.3. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP), NAP**

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Applicant: Instituto Grifols S.A. (Flebogamma DIF); CSL Behring GmbH (Hizentra, Hyqvia); Baxalta Innovations GmbH (Kiovig); Baxter AG (Privigen); various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of posterior reversible encephalopathy syndrome (PRES)

EPITT 18512– New signal

Lead Member State: DE

### **Background**

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin for subcutaneous administration is indicated as replacement therapy in adults and children (0-18 years) in primary immunodeficiency syndromes such as congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiency, IgG subclass deficiencies with recurrent infections; and as replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. Human normal immunoglobulin for intravenous administration is indicated for replacement therapy in adults, and children and adolescents (0-18 years) in primary immunodeficiency (PID) syndromes with impaired antibody production, hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic

antibiotics have failed, hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation, hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT) and congenital acquired immune deficiency syndrome (AIDS) with recurrent bacterial infections. In addition, human normal immunoglobulin for intravenous administration is also indicated as immunomodulation in adults, and children and adolescents (0-18 years) in primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count, Guillain-Barré syndrome, Kawasaki disease, and for some products for chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN).

During routine signal detection activities, a signal of posterior reversible encephalopathy syndrome (PRES) was identified by the EMA, based on 14 cases retrieved from EudraVigilance and one additional case published in the literature. Germany<sup>2</sup> 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 a causal relationship is probable in 7 cases, the PRAC agreed to request all the MAHs of intravenous (IV)Igs-containing medicinal products to provide a cumulative review of cases of PRES associated with IVIg treatment.

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

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

- The MAHs of human normal immunoglobulin-containing medicinal products should submit to the EMA, within 60 days, a cumulative review of cases of PRES associated with IVIg treatment. The MAHs should include data from spontaneous reporting, clinical trials as well as published literature (information on indication, administration dates, concomitant diseases, concomitant medication, confounding factors, and magnetic resonance imaging findings). This review should include all cases of PRES retrieved from the MAHs' safety databases since approval and should include the reporting rate for PRES for each product based on 1,000 kg of the sold product. Finally an analysis on the potential underlying patho-mechanisms of PRES with IVIg therapy should be addressed. The MAHs should discuss any potential amendment to the product information and/or to the risk management plan as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.1.4. Mercaptopurine - XALUPRINE (CAP); NAP**

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Applicant: Nova Laboratories Limited; Aspen Pharma; various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of lymphoproliferative disorders  
EPITT 18503– New signal  
Lead Member State: SE

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<sup>2</sup> Paul-Ehrlich-Institute

## Background

Mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides for cytotoxicity. Xaluprine, a centrally authorised product containing mercaptopurine, is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

During routine signal detection activities, a signal of lymphoproliferative disorders was identified by the EMA, based on 47 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## Discussion

Case reports from EudraVigilance and from the literature suggest that mercaptopurine could potentially be associated with an increased risk of lymphoproliferative disorders. The PRAC noted that azathioprine is the pro-drug of mercaptopurine. Therefore, this evaluation is also relevant for azathioprine, although it was acknowledged that there seems to be some information included in the product information on this risk, in at least some nationally authorised products containing azathioprine. Taking into account the available evidence, the PRAC agreed to request Aspen Pharma to provide cumulative reviews of lymphoproliferative disorders in association with mercaptopurine or azathioprine.

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

## Summary of recommendation(s)

- The MAH for Aspen Mercaptopurine and Imuran (Aspen Pharma) should submit to the EMA, within 60 days, cumulative reviews of lymphoproliferative disorders in association with mercaptopurine or azathioprine. The cumulative reviews should include all lymphoproliferative disorders and should be contextualised in relation to the occurrence of lymphoproliferative disorders in non-mercaptopurine/azathioprine-treated disease populations, according to the data and publications available. The MAH should also analyse the role of mercaptopurine and azathioprine in the development of haematophagic histiocytosis. The MAH should discuss the need for any potential amendment to the product information and/or the submission of risk management plans as applicable.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.1.5. Somatropin - NUTROPINAQ (CAP), OMNITROPE (CAP), SOMATROPIN BIOPARTNERS (CAP), NAP

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Applicant: Ipsen Pharma; Sandoz GmbH; BioPartners GmbH; various

PRAC Rapporteur: Torbjörn Callreus

Scope: Signal of hypersensitivity reactions

EPITT 18486 – New signal

Lead Member State(s): DK, DE, NL

## Background

Somatropin is a polypeptide hormone of recombinant DNA origin whose amino acid sequence is identical to that of human growth hormone (hGH) of pituitary origin.

Somatropin is indicated for the replacement therapy of endogenous growth hormone in childhood- or adult-onset growth hormone deficiency (GHD) under certain conditions.

The exposure for NutropinAq, a centrally authorised medicine containing somatropin, is estimated to have been more than 278,982 patients worldwide, in the period from first authorisation in 2011 until March 2014. The exposure for Omnitrope, a centrally authorised medicine containing somatropin, is estimated to have been more than 58,742,266 patient-days worldwide, in the period from first authorisation in 2006 until March 2014. The clinical trials exposure for Somatropin Biopartners, a centrally authorised medicine containing somatropin, is estimated to have been more than 711 patient-years worldwide, until March 2014.

During routine signal detection activities, a signal of hypersensitivity reactions was identified by the EMA, based on 34 cases retrieved from EudraVigilance. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC discussed the available evidence from the case reports in EudraVigilance. Taking into account that for 10 cases a causal relationship with somatropin was possible and that time to onset ranged from a few seconds to a month and a half, the PRAC agreed to request all the MAHs of somatropin-containing medicinal products to provide a cumulative review of cases of hypersensitivity reactions due to either somatropin or preservatives, including data from the literature and a discussion on the need for any potential amendment to the product information and/or the risk management plan.

The PRAC appointed Torbjörn Callreus as Rapporteur for the signal.

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

- All the MAHs of somatropin-containing medicinal products should submit to the EMA, in the next PSUR (DLP: 30/09/2015) (PSUSA/00002772/201509) a cumulative review of cases of hypersensitivity reactions due to either somatropin or preservatives, including data from the literature and a discussion on the need for any potential amendment to the product information and/or the risk management plan as applicable.

#### **4.1.6. Tigecycline – TYGACIL (CAP)**

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Applicant: Pfizer Limited

PRAC Rapporteur: Miguel-Angel Macia

Scope: Signal of hypofibrinogenaemia

EPITT 18479 – New signal

Lead Member State: ES

### **Background**

Tigecycline is a glycylicycline antibiotic indicated in adults and in children from the age of eight years for the treatment of complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections as well as for the treatment of complicated intra-abdominal infections (cIAI) under certain conditions.

The exposure for Tygacil, a centrally authorised medicine containing tigecycline, is estimated to have been more than 2,643,830 patients worldwide, in the period from first authorisation in 2006 until June 2014.

Following a recent publication<sup>3</sup> suggesting an association between tigecycline use and decrease in fibrinogen levels, a signal of hypofibrinogenaemia was identified by the EMA, based on 20 cases retrieved from EudraVigilance and one additional case published in the literature. 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 time to onset ranged between 0 and 24 days, that positive dechallenge was reported in several cases, but that most of the cases presented included confounding factors, the PRAC agreed to request the MAH to provide a cumulative review of all cases of coagulopathies and/or bleeding (in particular hypofibrinogenaemia) associated with tigecycline, including literature data.

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

- The MAH for Tygacil (tigecycline) should submit to the EMA, within 60 days, a cumulative review of all cases of coagulopathies and/or bleeding (in particular hypofibrinogenaemia), including literature data. The MAH should discuss possible confounding factors in these cases, as well as patients' characteristics including medical history, stage of the underlying disease and the tigecycline dose received, in order to evaluate potential risk factors. The MAH should also present a review of relevant preclinical data and discuss the potential mechanism in the light of all available data. If available, the MAH should present data on fibrinogen levels from clinical trials in the tigecycline and comparator groups. Finally, the MAH should discuss the need for any potential amendment to the product information and/or 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. Methotrexate - NAP**

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Applicant: various

PRAC Rapporteur: Doris Stenver

Scope: Signal of congenital cardiovascular anomaly  
EPITT 18481 – New signal  
Lead Member State(s): DK

### **Background**

Methotrexate is a folic acid antagonist classified as an antimetabolite cytotoxic agent indicated for the treatment of acute lymphocytic leukemia, non-Hodgkin's lymphoma,

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<sup>3</sup> Zhang Q., Zhou S. et al. 'Tigecycline treatment causes a decrease in fibrinogen levels', *Antimicrobial Agents and Chemotherapy*, 2015; 59 (3), 1650-1655.

osteogenic sarcoma, adjuvant treatment and in advanced breast cancer, metastatic or recurrent head and neck cancer, choriocarcinoma and similar trophoblastic diseases, advanced urinary bladder cancer, soft-tissue and osteogenic sarcomas, and solid tumours particularly breast, lung, head and neck, bladder, cervical, ovarian, and testicular carcinomas.

Following the publication of the study by *Dawson et al.*<sup>4</sup>, a signal of congenital cardiovascular anomaly was identified by EMA based on 16 cases of congenital anomalies reported in infants exposed to methotrexate in this study and a search in EudraVigilance. The reported congenital heart defects included atrial septal defects, tetralogy of Fallot, pulmonary valve stenosis, ventricular septal defects, and total anomalous pulmonary venous return. Denmark confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC noted the published study by *Dawson et al.* Taking into account the evidence regarding the risk of cardiovascular anomalies observed in children exposed in utero to methotrexate from the published literature, and also highlighted by disproportionality in reporting in EudraVigilance, and having noted some disharmonies in the product information for methotrexate at national level regarding human experience in pregnancy, the PRAC agreed to further assess the data available on pregnancy exposure with methotrexate in order to evaluate the need for updates to the product information, and to request the originator MAH for methotrexate to provide answers to a list of questions.

The PRAC appointed Doris Stenver as Rapporteur for the signal.

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

- The innovator MAH for methotrexate (Pfizer) should submit to the EMA, within 60 days, responses to a list of questions taking into consideration the data provided in the aforementioned studies as well as any relevant data which the MAH may hold and also based on a complementary search of the relevant literature.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### **4.2.2. Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); paroxetine (NAP); sertraline (NAP)**

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Applicant: various

PRAC Rapporteur: Isabelle Robine

Scope: Signal of congenital abnormalities after maternal use of an SSRI

EPITT 14082 – New signal

Lead Member State(s): DK, FR, NL, SE, UK

### **Background**

Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs) are a class of drugs which increase the extracellular level of the neurotransmitter serotonin in

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<sup>4</sup> Dawson AL, Riehle-Colarusso T, Reefhuis J, Arena JF, The National Birth Defects Prevention study. 2014. Maternal exposure to methotrexate and birth defects: A population based study. *Am J Med Genet Part A* 164A:2212-2216.

the brain by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They are typically used in the treatment of major depressive disorder and anxiety disorders.

Risks of congenital abnormalities after SSRI exposure during pregnancy had been previously reviewed in the EU. These reviews led to amendments of the product information for different substances regarding the risk of pulmonary hypertension and/or cardiovascular defects.

Following the publication by *Reefhuis J. et al.*<sup>5</sup> of an analysis combining results from independent published analyses with data from a multicentre population based case-control study of birth defects, a signal of increased risk of congenital abnormalities after maternal use of an SSRI was identified by France also based on several other publications (*Wemakor A. et al.*<sup>6</sup>, *Berard A. et al.*<sup>7</sup>, *Yazdy et al.*<sup>8</sup>). France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### Discussion

Based on the publication by *Reefhuis et al.* on the increased risk of congenital abnormalities other than cardiovascular, associated with SSRIs, as well as those of other recent publications, the PRAC agreed that the evidence is insufficiently robust to warrant further investigation at this stage. Therefore the MAHs of all SSRIs should continue to monitor the foetal risk after in-utero exposure to SSRIs, including risks of congenital abnormalities, as part of routine safety surveillance.

The PRAC appointed Isabelle Robine as Rapporteur for the signal.

### Summary of recommendation(s)

- The MAHs of all SSRIs should continue to monitor the risk after in-utero exposure to SSRIs, including the risk of congenital abnormalities, as part of routine safety surveillance.

#### 4.2.3. Selective serotonin reuptake inhibitors (SSRIs): citalopram (NAP); duloxetine (NAP); escitalopram (NAP); fluoxetine (NAP); fluvoxamine (NAP); mirtazapine (NAP); paroxetine (NAP); sertraline (NAP); venlafaxine (NAP)

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Applicant: various

PRAC Rapporteur: Isabelle Robine

Scope: Signal of risk of autistic spectrum disorders (ASD) after maternal use of SSRI

EPITT 14082 – New signal

Lead Member State(s): DK, FR, NL, SE, UK

### Background

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<sup>5</sup> Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA; National Birth Defects Prevention Study. Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. *BMJ*. 2015 Jul 8; 351:h3190

<sup>6</sup> Wemakor A, Casson K, Garne E, et al. Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. *Eur J Epidemiol* 2015

<sup>7</sup> Berard A, Zhao J-P, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. *Am J Obstet Gynecol* 2015;212:795

<sup>8</sup> Yazdy, Mahsa M.; Mitchell, Allen A.; Louik, Carol; Werler, Martha M. Use of Selective Serotonin-Reuptake Inhibitors During Pregnancy and the Risk of Clubfoot. *Epidemiology*. 2014 Nov;25(6):859-65



Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs) are a class of drugs which increase the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with pure SSRIs having only weak affinity for the norepinephrine and dopamine transporters. They are typically used in the treatment of major depressive disorder and anxiety disorders.

Following the publication of the first systematic review and meta-analysis of SSRI use in pregnancy on the risk of ASD in children<sup>9</sup>, a signal of autistic ASD after maternal use of SSRI was identified by France. France confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

The PRAC noted the recent published review by *Man K.C. et al.*, the first systematic review and meta-analysis of SSRI use in pregnancy and risk of ASD in children, in which the authors concluded that this meta-analysis and the narrative review from two cohort studies supported an increased risk of ASD in children of mothers exposed to SSRIs during pregnancy. The PRAC agreed that this study had a number of limitations and noted other publications with conflicting results, nevertheless it was agreed that it would be important to further review the available information on a possible association of neurodevelopmental disorders, including ASD, following the use of SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) during pregnancy. Therefore the PRAC agreed to request all the MAHs of SSRIs and SNRIs to provide a cumulative review of data on neurodevelopmental disorders including ASD, reported after SSRI/SNRI use during pregnancy, from all relevant available data sources, including a critical discussion of the results, and an analysis of the effects of potential confounders on the neurocognitive outcomes in the child.

The PRAC appointed Isabelle Robine as Rapporteur for the signal.

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

- The MAHs of citalopram and escitalopram (Lundbeck), duloxetine and fluoxetine (Eli Lilly), fluvoxamine (Abbott), paroxetine (GSK), mirtazapine (Organon) and sertraline and venlafaxine (Pfizer) should submit to the EMA, within 90 days, a cumulative review of data on neurodevelopmental disorders including ASD, reported after SSRI/SNRI use during pregnancy, from all relevant available data sources (post-marketing data, pharmacoepidemiological studies, and the published literature). This review should include a critical discussion of the results, including an analysis of the effects of potential confounders on the neurocognitive outcomes of the child (e.g. parental background disease, genetic, social, and environmental factors). Considering the studies identified by this review, the MAHs should discuss the possibility of performing a critical meta-analysis. A discussion of the evidence for a biologically plausible mechanism for involvement of an SSRI/SNRI in the aetiology of neurodevelopmental effects, including autistic spectrum disorder or effects on verbal and non-verbal abilities should also be included. Finally the MAHs should provide an overview, per EU member state, of the usage patterns of the respective SSRI/SNRI for which the MAH is responsible, in pregnant women, as available. Based on the review above, the MAHs

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<sup>9</sup> Man K.C. et al. Exposure to SSRI during pregnancy and risk of autism spectrum disorder in children: A systematic review and meta-analysis of observational studies. *Neuroscience and Biobehavioral Reviews* 49 (2015) 82–89

should also discuss the need for any potential amendment to the product information and/or risk management plan as applicable.

- The Lead Member States for individual substances should provide an assessment report to the PRAC and to Isabelle Robine, the overall lead Rapporteur, within 60 days.
- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.3. Signals follow-up and prioritisation

#### 4.3.1. Aflibercept - EYLEA (CAP) – EMEA/H/C/002392/SDA/012

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Isabelle Robine

Scope: Signal of higher systemic exposure compared to ranibizumab after intravitreal injection

EPITT 18112 – Follow-up to March 2015

#### **Background**

For background information, see [PRAC minutes October 2014](#) and [PRAC minutes March 2015](#). The MAH replied to the request for information on the signal of higher systemic exposure compared to ranibizumab after intravitreal injection and provided a draft study protocol for post-authorisation safety study 15971 LIBRA (Long-term Investigation and risk-Benefit analysis of the Real-life utilisation of Aflibercept in macular disease). The responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC discussed the MAH's responses as well as all the data and information available on the signal of higher systemic exposure compared to ranibizumab after intravitreal (IVT) injection.

The MAH submitted an updated cumulative review of the signal including non-clinical, clinical, pharmacoepidemiological and post-marketing data. The MAH was also asked to submit a revised protocol for a PASS, which is already included in the pharmacovigilance plan of the Eylea EU-RMP to address important potential systemic risks such as arterial thromboembolic events. These potential risks are already addressed in sections 4.4 and 4.8 of the Eylea SmPC. The MAH was of the view that based on the totality of the data there is no safety signal.

Based on the totality of submitted data, the PRAC concluded that there is no clinically relevant safety signal and that a comparative study is therefore not necessary.

The PRAC will assess the above mentioned draft protocol submitted by the MAH within the appropriate post-authorisation measure procedure.

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

- Having considered the strengths and limitations of all relevant data, including clinical, non-clinical and pharmacokinetic data, the PRAC concluded that there is no safety signal.

#### 4.3.2. Human fibrinogen, human thrombin – TACHOSIL (CAP) - EMEA/H/C/000505/SDA/041

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Applicant: Takeda Austria GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of intestinal obstruction  
EPITT 18373 – 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 intestinal obstruction 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 endorsed the MAH's proposal to update the RMP to include gastrointestinal obstruction as a new important identified risk and to update sections 4.4, 4.8 and 6.6 of the SmPC. The PRAC agreed to request the MAH to provide a proposal for wording for sections 4.4 and 6.6 of the SmPC and to comment on a draft wording for section 4.8. In addition, in order to raise awareness among concerned healthcare professionals in the EU, including surgeons, and to promote reporting of any suspected adverse reactions, the PRAC recommended that the MAH for TachoSil provides a draft Direct Healthcare Professional Communication (DHPC) letter including a draft communication and key elements for educational materials with the description of the new risk(s).

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

- The MAH for TachoSil (human fibrinogen/human thrombin) should submit to the EMA, within 15 days, a proposal for wording to update sections 4.4 and 6.6 of the SmPC and comment on the draft wording for section 4.8 of the SmPC. In addition the MAH for TachoSil should submit a draft DHPC letter including a draft communication plan; and key elements for educational materials with the description of the new risk(s).

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

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Applicant: Nicobrand Limited

PRAC Rapporteur: Veerle Verlinden

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

##### **Background**

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

##### **Discussion**

The PRAC discussed the MAH's responses. Having reviewed the cumulative review of cases submitted by the MAH, including the plausible latency and cases of positive de- and re-

challenge, along with the evidence from clinical trials and a plausible biological mechanism, the PRAC agreed that a causal relationship between topical oxybutynin and psychiatric disorders cannot be excluded. The proposal by the MAH to update the product information is endorsed. The PRAC agreed to request the MAH to provide a calculation of the frequencies of the psychiatric related adverse drug reactions: anxiety disorders (e.g. anxiety, nervousness, panic reaction and agitation), delirium and psychotic disorders (e.g. confusion, hallucinations and disorientation), insomnia and cognitive disorders (e.g. memory impairment, amnesia, lethargy, disturbance in attention), to be added to the product information in line with the SmPC guideline. The MAH should also make a proposal for the package leaflet in line with the SmPC. Finally the PRAC agreed to consult the Paediatric Committee (PDCO) on the use of oxybutynin in the paediatric population.

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

- The MAH for Kentera (oxybutynin) should submit to the EMA, within 30 days, a calculation of the frequencies of the psychiatric related adverse drug reactions: anxiety disorders (e.g. anxiety, nervousness, panic reaction and agitation), delirium and psychotic disorders (e.g. confusion, hallucinations and disorientation), insomnia and cognitive disorders (e.g. memory impairment, amnesia, lethargy, disturbance in attention), to be added to the product information in line with the SmPC guideline. The MAH should also make a proposal for the package leaflet in line with the SmPC.

#### **4.3.4. Palifermin – KEPIVANCE (CAP) - EMEA/H/C/000609/SDA/054**

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Applicant: Swedish Orphan Biovitrum AB

PRAC Rapporteur: Rafe Suvarna

Scope: Signal of infection  
EPITT 18401 – 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 infection and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC discussed the MAH's responses. Taking into account the data submitted by the MAH, the PRAC agreed that there was sufficient evidence to recommend an update of sections 4.2, 4.4 and 5.1 of the SmPC. A key recommendation related to the gap between the two sets of palifermin dosing (before and after 'conditioning' treatment), as there is evidence that the risk of infection may be increased if the gap is too short. Based on data from the pivotal phase II and III studies and current EU radiochemotherapy conditioning regimens, section, 4.2 ('posology and method of administration') of the SmPC should be updated to clarify that Kepivance is indicated specifically for use in combination with radiochemotherapy conditioning regimens. Section 4.4 (Special warnings and precautions for use) of the SmPC should also be updated with detailed information regarding the increased risk of infection with high dose melphalan and a statement that the efficacy and safety have only been established in association with a conditioning regimen that comprised total body irradiation and high-dose chemotherapy (cyclophosphamide and etoposide). In

addition section 5.1 (Pharmacodynamic properties) should be updated with further information on the posology used in the pivotal Phase III study.

Considering the agreed change in the posology regimen aimed at minimising the risk of infection with Kepivance, the PRAC agreed that the MAH should prepare a detailed communication plan including a Direct Healthcare Professional Communication (DHPC) letter to alert HCPs. To assess the adherence to the new recommendation and to establish how palifermin is used in clinical practice in the EU, the MAH is requested to perform a drug utilisation study as an additional pharmacovigilance activity. Finally the PRAC requested the MAH to update the RMP and combine the important potential risks of 'oral candidiasis', 'sepsis' and 'bacteraemia' into 'infections (including sepsis).' Other parts of the RMP should be updated accordingly. Because it is questionable whether the non-clinical, mechanistic studies proposed by the MAH will provide a better understanding of the potential risk of infection which might impact on the clinical advice, the PRAC considered these studies as voluntary (and not category 3). The PRAC has recommended the changes to be implemented within a type II variation and submitted within 2 months.

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

- The MAH for Kepivance (palifermin) should submit to the EMA, within 60 days, a type II variation to update sections 4.2, 4.4 and 5.1 of the SmPC with regard to the risk of infection and to update the posology. The MAH should submit with this type II variation a draft (DHPC) letter including a draft communication plan. To assess the adherence to the new recommendation and to establish how palifermin is used in clinical practice in the EU, the MAH should perform a drug utilisation study as an additional pharmacovigilance activity. Finally the MAH should update the RMP and combine the important potential risks of 'oral candidiasis', 'sepsis' and 'bacteraemia' into 'infections (including sepsis).' Other parts of the RMP should be updated accordingly.

#### **4.3.5. Warfarin (NAP)**

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Applicant: various

PRAC Rapporteur: Torbjörn Callreus

Scope: Signal of bone density decrease  
EPITT 18173 – Follow-up to July 2015

#### **Background**

For background information, see [PRAC minutes March 2015](#) and [PRAC minutes July 2015](#). The MAHs replied to the request for information on the signal of bone density decrease and the responses were assessed by the Rapporteur.

#### **Discussion**

The PRAC considered the advice of the Paediatric Committee (PDCO) regarding the need to further assess the potential effects on bone mineral density associated with long-term treatment with warfarin in children, in order to fully evaluate the strengths and limitations of the evidence provided by the studies by *Monagle et al.*<sup>10</sup>, and *Barnes et al.*<sup>11</sup>. Having

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<sup>10</sup> Monagle K., Jones S, King I et al. Anticoagulation of cardiomyopathy in children. *Thrombosis research*. May 10, 2014; 134:255-258.

assessed the responses provided by the MAHs, based on reviews of the published literature and of their safety databases, the PRAC considered that the overall findings do not currently provide sufficient evidence to confirm a causal association between warfarin and a decrease in bone mineral density in children following long-term exposure. The PRAC therefore agreed that no updates of product information or additional risk minimisation measures are needed at this point of time. The MAHs of warfarin-containing medicinal products are requested to keep this issue under routine monitoring safety surveillance.

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

- The MAHs of warfarin-containing medicinal products should continue to monitor cases of bone density decrease as part of routine safety surveillance.

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

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

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

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

See also Annex I. 14.1.

#### **5.1.1. Albutrepenonacog alfa - EMEA/H/C/003955, Orphan**

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Applicant: CSL Behring GmbH

Scope: Prophylaxis and treatment of bleeding in all patients with haemophilia

#### **5.1.2. Eptifibatide - EMEA/H/C/004104**

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Generic

Scope: Prevention of early myocardial infarction

#### **5.1.3. Factor X - EMEA/H/C/003855, Orphan**

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Applicant: Bio Products Laboratory

Scope: Treatment of factor X deficiency

#### **5.1.4. Grazoprevir, elbasvir - EMEA/H/C/004126**

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Scope: Treatment of chronic hepatitis C (CHC) in adults

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<sup>11</sup> Barnes C, Newall F, Ignjatovic V, et al. reduced bone density in children on long-term warfarin. *Pediatric Res* 2005; 57:578-581.

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

See also Annex I. 14.2.

### 5.2.1. Orlistat – ALLI (CAP) - EMEA/H/C/000854/II/0052

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Rafe Suvarna

Scope: Submission of a revised RMP in order to update the safety concerns, pharmacovigilance plan and risk minimisations measures and to replace PASS study RH01159 (survey 4) with PASS study 204675

#### Background

Orlistat is a gastrointestinal lipase inhibitor indicated for weight loss in adults who are overweight (body mass index, BMI  $\geq 28$  kg/m<sup>2</sup>) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

The PRAC is evaluating a type II variation procedure for Alli, a centrally authorised medicine containing orlistat, to update the RMP to propose an alternative study PASS 204675<sup>12</sup> to survey RH01159<sup>13</sup> and the MAH had submitted a protocol accordingly. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

#### Summary of advice

- The RMP version 14 for Alli (orlistat) in the context of the variation under evaluation by the PRAC and CHMP is considered acceptable as detailed in the adopted assessment report.
- The PRAC considered that the objectives of the proposed PASS should also include all special warnings and precautions for use that require patients to consult a doctor before taking Alli, or the MAH should justify their exclusion from the objectives. In order to minimise the risk of selection bias, the protocol should include giving instructions on the prerequisites for staff to participate. The success criteria should be discussed further in the study protocol, both for the primary and secondary endpoints. In particular, the MAH should outline how the results of the study will link to the need for further action, placing particular emphasis on endpoints that relate to important safety issues. The results for the primary and secondary endpoints should be stratified by EU country, as well as presented overall for the EU population.

### 5.2.2. Sevelamer – RENAGEL (CAP) - EMEA/H/C/000254/WS/0803; RENVELA (CAP) - EMEA/H/C/000993/WS/0803; SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/WS/0803; TASERMITY (CAP) - EMEA/H/C/003968/WS/0803

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Veerle Verlinden

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<sup>12</sup> Evaluation of the effectiveness of the revised alli pack information in helping pharmacy staff within the EU supply alli appropriately. Protocol comprises an online questionnaire on a series of virtual customers to include both customers who are suitable and suitable for alli

<sup>13</sup> Survey to measure the effectiveness of the routine risk minimisation measures based on the use of a questionnaire handed to pharmacists at the point of sale



Scope: Update of the RMPs to reflect a single list of safety concerns for both sevelamer formulations as per the PRAC request, as the safety profile of both compounds is similar; list of safety concerns in the RMP aligned with the list of safety concerns of the PBRER as per the PRAC request; two formulations (sevelamer hydrochloride and sevelamer carbonate) in one single RMP document; addition of risk minimisation measures reflecting the agreement of a single list of safety concerns for both sevelamer formulations are simplified; educational material proposed addressing the prevention of vitamin deficiency for both sevelamer formulations; addition as a newly identified safety concern, the risk of 'hypersensitivity reactions, including angioedema and anaphylactic reactions'

## Background

Sevelamer is a non-absorbed phosphate binding crosslinked polymer free of metal and calcium indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis as well as in adult patients with chronic kidney disease not on dialysis with serum phosphorus  $\geq 1.78$  mmol/l under certain conditions.

The PRAC is evaluating a worksharing variation procedure for Renagel, Renvela, Sevelamer Carbonate Zentiva and Tasermyt, centrally authorised medicines containing sevelamer, to update the RMP to reflect a single list of safety concerns for both formulations of sevelamer-containing products (sevelamer hydrochloride and sevelamer carbonate) and aligned to the list of safety concerns assessed in the most recent PSUSA procedure (PSUSA/02697/201410, see [PRAC minutes June 2015](#)). In addition, the risk minimisation measures are simplified reflecting the agreement of a single list of safety concerns for both formulations. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this worksharing variation.

## Summary of advice

- The RMP version 7 for Renagel, Renvela, Sevelamer Carbonate Zentiva and Tasermyt (sevelamer) in the context of the worksharing variation under evaluation by the PRAC and CHMP is considered acceptable provided that an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that the MAH should provide an updated RMP including the deletion of the educational material addressing the prevention of vitamin deficiency for both sevelamer formulations.

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

See also Annex I. 14.3.

### 5.3.1. [Deferasirox – EXJADE \(CAP\) - EMEA/H/C/000670/X/0043](#)

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Corinne Fechant

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

## Background

Deferasirox is an iron chelating agent indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major, for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in some specific sub-populations, as well as for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes under certain conditions.

The CHMP is evaluating a line extension for Exjade, a centrally authorised product containing deferasirox, for a new pharmaceutical form and new strengths (Exjade 90, 180 mg and 360 mg film-coated tablets). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this line extension procedure. For further background, see [PRAC minutes July 2015](#).

### Summary of advice

- The RMP version 10.1 for Exjade (deferasirox) in the context of the line extension under evaluation by the CHMP was considered acceptable provided that an updated RMP and satisfactory responses to the PRAC list of questions are submitted.
- The PRAC considered that the risk of medication error related to the film-coated formulation remains and should be considered as 'missing information'. In addition, the MAH should add the ongoing study F2201<sup>14</sup> to the list of additional pharmacovigilance activities in order to better characterize the safety profile of the new formulation. Moreover, the MAH should propose additional pharmacovigilance activities for the new formulation used in the youngest children (particularly under 6 years) to better characterize the paediatric safety profile. See also under 7.1.1. In terms of additional risk minimisation measures, the MAH should propose ways to ensure the current and new formulations are well-distinguished in terms of outer cartons, blisters and tablets. Moreover, the MAH should propose educational material for patients and HCPs (prescribers, pharmacists) for both formulations for all indications in order to minimise any risk of medication errors between the two formulations. Finally, the PRAC considered that a prescribers' survey would be essential to assess awareness amongst prescribers of the different posology and methods of administration between the two formulations.

### 5.3.2. Etanercept – ENBREL (CAP) - EMEA/H/C/000262/II/0184

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Applicant: Pfizer Limited

PRAC Rapporteur: Rafe Suvarna

Scope: Update of section 4.6 of the SmPC in order to update the information on the effects of etanercept on pregnancy and lactation. The Package Leaflet and the RMP are updated accordingly. In addition, the MAH took the opportunity to update the RMP in reference to past approved variations

#### Background

Etanercept is a tumour necrosis factor alpha (TNF- $\alpha$ ) inhibitor indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis,

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<sup>14</sup> Study evaluating adverse event incidence between formulations in a patient population over a 6 months treatment period

non-radiographic axial spondyloarthritis, ankylosing spondylitis (AS) and plaque psoriasis under certain conditions.

The CHMP is evaluating a type II variation procedure for Enbrel, a centrally authorised product containing etanercept, to update the safety information on the effects of etanercept on pregnancy and lactation, based on data from the Organisation of Teratology Information Specialists (OTIS) registry, MAH's pharmacovigilance database, clinical trials and published literature. The RMP is updated accordingly, including data from previously assessed variations, in particular results from the Systematic Tracking of Real Kids (STORK) study. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see [PRAC minutes June 2015](#) and [PRAC minutes September 2015](#).

#### **Summary of advice**

- The RMP version 5.4 for Enbrel (etanercept) in the context of the variation under evaluation by the CHMP was considered acceptable.
- The PRAC considered that the MAH should submit to EMA, within 90 days, a PASS protocol for an observational study (category 3) to further investigate the relationship between etanercept exposure and major birth defects, along with proposed study timelines and reporting milestones. This study should be recorded in the RMP. The PRAC suggested some refinements in the proposed changes in the product information for consideration by the CHMP.

### **5.3.3. Natalizumab – TYSABRI (CAP) - EMEA/H/C/000603/II/0077**

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Applicant: Biogen Idec Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adults with highly active relapsing remitting multiple sclerosis with high disease activity despite treatment with at least one modifying therapy (DMT). As a consequence, sections 4.1 and 4.4 of the SmPC are updated in order to provide physicians with more options for treating relapsing remitting multiple sclerosis (RRMS) patients with high disease activity who fail an initial disease modifying therapy (DMT). Consequential changes to SmPC sections 4.2, 4.3, 5.1 and Package Leaflet are submitted accordingly

#### **Background**

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

The CHMP is evaluating an extension of the therapeutic indication for Tysabri, a centrally authorised product containing natalizumab, to include a new indication for the treatment of adult patients pretreated with at least one disease modifying therapy (DMT). The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this type II variation. For further background, see [PRAC minutes June 2015](#).

#### **Summary of advice**

- The RMP version 18 for Tysabri (natalizumab) in the context of the line extension under evaluation by the CHMP should be updated<sup>15</sup> to incorporate the specific safety issues of the indication proposed in the variation, in particular, missing information on the risk of progressive multifocal leukoencephalopathy (PML). The revised RMP should reflect the changes to the new product information. In addition, the MAH should discuss the need to update the educational material accordingly. Finally, the MAH should propose a non-interventional PASS (category 3) aimed at determining the risk of PML in patients who were previously treated with at least one DMT. The MAH should discuss the possible methodological study designs and their feasibility, as well as the possibility to involve existing registries in the study proposal.

## 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. Bortezomib – VELCADE (CAP) - PSUSA/00424/201504

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

#### Background

Bortezomib is a proteasome inhibitor indicated in adults, alone or in combination, for the treatment of patients with progressive multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation, of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation, for the induction treatment of patients with untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation as well as for the treatment of patients with untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Velcade, centrally authorised medicines containing bortezomib, 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 Velcade (bortezomib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add the preferred term small intestine obstruction to the undesirable effect gastrointestinal obstruction already

<sup>15</sup> Without prejudice to the outcome of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 (see 3.2.2.)

included in the undesirable effects section of the SmPC. Therefore the current terms of the marketing authorisation(s) should be varied<sup>16</sup>.

- The MAH should be requested to submit to the EMA, within 60 days, a cumulative review of all progressive multifocal leukoencephalopathy (PML) cases, including a causality assessment for each of them. In conducting this critical analysis, the MAH should consider the recent publication on the strategy for regulatory decision-making for management of PML<sup>17</sup> and propose if appropriate a statement to be included in section 4.8 of the SmPC.

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

### 6.1.2. Ceftaroline fosamil – ZINFORO (CAP) - PSUSA/10013/201504

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Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Ceftaroline fosamil is an antibacterial indicated in adults for the treatment of complicated skin and soft tissue infections (cSSTI) and for the treatment of community-acquired pneumonia.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zinforo, centrally authorised medicines containing ceftaroline fosamil, 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 Zinforo (ceftaroline fosamil) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include eosinophilia as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>18</sup>.
- In the next PSUR, the MAH should provide an updated review of cases suggestive of drug reaction with eosinophilia and systemic symptoms (DRESS).
- The MAH should be requested to amend the list of safety concerns in the next RMP update to reflect the outcome of approved variations pertaining to the following missing information: use in patients with pre-existing severe renal impairment; use in the paediatric population and potential for suboptimal dosing in patients with more severe more serious systemic inflammation.

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<sup>16</sup> Update of SmPC section 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

<sup>17</sup> Segec A., Keller-Stanislawski B., Vermeer N.S., Macchiarulo C., Straus S.M., Hidalgo-Simon A. and De Bruin M.L.; Strategy in Regulatory Decision-Making for Management of Progressive Multifocal Leukoencephalopathy; Clin Pharmacol Ther. 2015 Nov;98(5):502-5. doi: 10.1002/cpt.199

<sup>18</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

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.

### 6.1.3. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP) - PSUSA/01745/201504

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Applicant: Novartis Influenza Vaccines Marburg GmbH

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) is indicated for the prophylaxis of influenza in adults, especially in those who are at an increased risk of associated complications.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Optaflu, a centrally authorised influenza vaccine, 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 Optaflu (influenza vaccine (surface antigen, inactivated, prepared in cell cultures)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include paraesthesia as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>19</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.

### 6.1.4. Lurasidone – LATUDA (CAP) - PSUSA/10114/201504

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Qun-Ying Yue

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Lurasidone is a selective blocking agent of dopamine and monoamine effects indicated for the treatment of schizophrenia in adults aged 18 years and over.

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<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 CHMP for adoption of an opinion

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Latuda, a centrally authorised medicine containing lurasidone, 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 Latuda (lurasidone) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include tardive dyskinesia as new undesirable effect with an uncommon frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.
- The MAH should be requested within the next RMP update to upgrade tardive dyskinesia from an important potential risk to an identified risk under extrapyramidal symptoms.

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. Mannitol – BRONCHITOL (CAP) - PSUSA/09226/201504**

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Applicant: Pharmaxis Pharmaceuticals Limited

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Mannitol is a hyperosmotic agent indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bronchitol, a centrally authorised medicine containing mannitol, 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 Bronchitol (mannitol) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to improve the clarity of the wording regarding the need for patients to complete the initiation dose assessment before starting treatment in order to assess patients for bronchial hyper-responsiveness. The changes will be made in the posology and method of administration and in the special warnings and precautions sections. Therefore the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.

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<sup>20</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>21</sup> Update of SmPC sections 4.2 and 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion



- Given that there are limited data from the use of mannitol in pregnant women (less than 300 pregnancy outcomes) and the SmPC advises caution in the use of mannitol in pregnancy, the outcome of the pregnancy case reported during this interval should be updated in the next PSUR. The MAH should also explain how patients who have a low (Forced Expiratory Volume) FEV1 at start of treatment (which appear to be coded as 'FEV decreased') are distinguished from those who experience a decrease in FEV during treatment. If not completed within the next reporting interval, the MAH is requested to provide an update on the progress made with redistribution of the revised HCP education pack and the predicted date for the final HCP survey.
- The MAH should be requested to include starting Bronchitol treatment without completing the full Bronchitol initiation dose assessment (BIDA) as an important potential risk with the next RMP update.

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. Nintedanib – OFEV (CAP) - PSUSA/10319/201504

Applicant: Boehringer Ingelheim Pharma GmbH & Co. KG

PRAC Rapporteur: Viola Macolic Sarinic

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Nintedanib is a tyrosine kinase inhibitor (TKI) indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ofev, a centrally authorised medicine containing nintedanib, 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 Ofev (nintedanib) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include cases of haemorrhage that have been reported in the post-marketing period, including in patients with or without anticoagulant therapy or other drugs that could cause bleeding, in the special warnings and precautions for use section. In addition the product information should be updated to add epistaxis as new undesirable effect with a common frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should describe the criteria for assigning cases to HCP (healthcare professional) confirmed and HCP not confirmed groups from the patient support programmes. The MAH should closely monitor cases from SOCs<sup>23</sup> cardiac

<sup>22</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>23</sup> MedDRA system organ class

disorder, eye disorder, cerebrovascular accident, perforation and arterial thromboembolism and describe all relevant fatal cases. The MAH should also provide a cumulative review of all cases of renal failure and related events, including a discussion of OFEV-related risk factors such as cases of diarrhoea or vomiting leading to renal injury. The MAH should provide an update on the status of the study protocol and/or study 1199.229 'open-label drug-drug interaction study to evaluate pharmacokinetics of nintedanib and pirfenidone in patients with IPF' which is a part of additional pharmacovigilance activities. Finally the MAH should provide a cumulative review of all bleeding events with appropriate statistical analysis to better characterise the role of nintedanib versus concomitant anticoagulants in these events.

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. Sunitinib – SUTENT (CAP) - PSUSA/02833/201504

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Applicant: Pfizer Limited

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

#### **Background**

Sunitinib is a tyrosine kinase inhibitor (TKI) indicated in adults for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST), for the treatment of advanced/metastatic renal cell carcinoma (MRCC) and for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sutent, a centrally authorised medicine containing sunitinib, 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 Sutent (sunitinib) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide detailed reviews of cases of intestinal obstruction by indication and of cases of pneumatosis intestinalis and discuss the need for an update of the product information as appropriate. The MAH should also provide a cumulative review of diabetes cases and explain all the different cases for therapeutic indication. Furthermore, the MAH should review all reports of drug interactions between warfarin and sunitinib with a view to update the product information as appropriate. Cases of anaphylaxis should be also discussed in depth. Finally, the MAH should discuss in the section 'drug interaction' all cases regarding interaction between sunitinib and P-glycoprotein and breast cancer resistance protein (BCRP) substrates providing specific review reports.

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. Temsirolimus – TORISEL (CAP) - PSUSA/02887/201503

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Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope of procedure: Evaluation of a PSUSA procedure

##### **Background**

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin) indicated for the treatment of the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) and for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Torisel, a centrally authorised medicine containing temsirolimus, 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 Torisel (temsirolimus) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include new warnings on myocardial infarction, anaemia and malignancies. Therefore the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.
- In the next PSUR, the MAH should discuss the impact of underlying hyperglycaemia/diabetes mellitus on hyperglycaemia and the impact of underlying hypercholesterolemia on hypercholesterolemia/hyperlipidaemia and cardiovascular disorders such as myocardial infarction. The MAH should review and discuss the available data on cholecystitis, cholelithiasis and pancreatitis and their association to exposure to temsirolimus.
- The MAH should be requested to add myocardial infarction and malignancies as important potential risks with the next RMP update.

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.

#### 6.1.9. Thiotepa – TEPADINA (CAP) - PSUSA/02932/201503

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Applicant: Adienne S.r.l. S.U.

PRAC Rapporteur: Corinne Fechant

Scope of procedure: Evaluation of a PSUSA procedure

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<sup>24</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

## Background

Thiotepa is an antineoplastic agent indicated in combination as a conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients as well as when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Tepadina, a centrally authorised medicine containing thiotepa, 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 Tepadina (thiotepa) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- It was noted that encephalopathy is already included in the SmPC of Tepadina as a possible adverse reaction. The MAH should be requested to submit to the EMA, within 60 days, a detailed review of cases of leukoencephalopathy, discuss if there is a specific identified pattern of leukoencephalopathy and discuss the cases against the other types of encephalopathies such as progressive multifocal leukoencephalopathy (PML) and posterior reversible encephalopathy syndrome (PRES). The MAH should comment on whether there is any pathological mechanism of action that could explain the onset of leukoencephalopathy (e.g. toxic action, immunosuppressive action, underlying disease). The MAH should consider updating the product information and/or develop additional risk minimisation measures as appropriate.

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

### 6.1.10. Vandetanib – CAPRELSA (CAP) - PSUSA/09327/201504

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Applicant: AstraZeneca AB

PRAC Rapporteur: Corinne Fechant

Scope of procedure: Evaluation of a PSUSA procedure

## Background

Vandetanib is a protein kinase inhibitor indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Caprelsa, centrally authorised medicines containing vandetanib, 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 Caprelsa (vandetanib) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to amend the current warning on skin reactions to include that referral of the patient to seek urgent medical advice is recommended for severe skin reactions. Therefore the current terms of the marketing authorisation(s) should be varied<sup>25</sup>.
- In the next PSUR, the MAH should discuss adverse reaction case reports with a fatal outcome. In addition, the MAH should continue to discuss cases of QT prolongation reported from post marketing sources with regards to section 4.4 special warnings and precautions for use of the SmPC related to this safety concern.

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. Bimatoprost – LUMIGAN (CAP), NAP - PSUSA/00413/201503

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Applicant: Allergan Pharmaceuticals Ireland

PRAC Rapporteur: Torbjorn Callreus

Scope of procedure: Evaluation of a PSUSA procedure

#### Background

Bimatoprost, a potent ocular hypotensive agent, is a synthetic prostamide, structurally related to prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) that does not act through any known prostaglandin receptors. Bimatoprost is indicated for the reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to ophthalmic beta-blockers).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lumigan, a centrally authorised medicine containing bimatoprost, and nationally authorised medicines containing bimatoprost 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 bimatoprost-containing medicinal products in the approved indications remains favourable.
- Nevertheless, the product information of all bimatoprost formulations should be updated to include asthma, asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, dyspnoea and hypersensitivity reaction signs and symptoms of eye allergy and allergic dermatitis as new undesirable effects with an unknown frequency. In addition the product information of bimatoprost 0.01%

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<sup>25</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

formulations should be updated to include iris hyperpigmentation, macular oedema, blepharal pigmentation, periorbital and lid changes including deepening of the eyelid sulcus and dry eye as new undesirable effects with an unknown frequency. Therefore the current terms of the marketing authorisations should be varied<sup>26</sup>.

- The MAHs which have an RMP in place should be requested to upgrade acute asthma and asthmatic symptoms as important identified risks and to remove reactivation of corneal infiltration from the list of important potential risks 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.

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

See also Annex I. 15.3.

#### 6.3.1. Cabergoline (NAP) - PSUSA/00477/201503

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Applicant: various

PRAC Lead: Carmela Macchiarulo

Scope: Evaluation of a PSUSA procedure

#### **Background**

Cabergoline is an ergot derivate and a dopamine D2-agonist indicated for the treatment of inhibition/suppression of physiologic lactation, for the treatment of hyperprolactinemic disorders as well as in patients with prolactin-secreting pituitary adenomas, idiopathic hyperprolactinemia, or empty sella syndrome with associated hyperprolactinemia under certain conditions. Cabergoline is also indicated in the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicine containing cabergoline, 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 cabergoline-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, in order to better characterise the cardiac valve fibrotic risk, Pfizer is requested to stratify per indication cumulative data for the adverse drug reactions aortic valve incompetence, aortic valve sclerosis, cardiac failure, cardiac valve disease, heart valve incompetence, mitral valve incompetence, tricuspid valve incompetence to

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<sup>26</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

allow estimation of reporting rate. The MAHs should provide a cumulative analysis of cardiovascular side effects (such as heart attack and stroke), neurological side effects such as seizures (fits) and psychiatric side effects (such as hallucinations, psychosis and manic episodes) with particular consideration of a possible role of puerperal, post-partum and uncontrolled 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.

### 6.3.2. Calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, sodium hydroxide (NAP) - PSUSA/09162/201503

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Applicant: various

PRAC Lead: Maria Popova-Kiradjieva

Scope: Evaluation of a PSUSA procedure

#### **Background**

Medicinal products containing calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, and sodium hydroxide constitute an extracellular type solution for solid organ preservation used in static cold storage preservation techniques to reduce ischemic injury following explantation from the donor, by rapid cooling of the organ(s). Cooling reduces cellular metabolism and oxygen requirements but at the same time is related to induction of cell swelling and cytoskeletal alterations. Of major importance during transplantation is the risk of ischemia reperfusion injury (IRI) which includes lesions related to hypothermia and hypoxia during ex vivo preservation of the graft and to the re-warming associated with reoxygenation during reperfusion.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicinal products containing calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, and sodium hydroxide, 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 calcium chloride, glutamic acid, glutathione, histidine, lactobionic acid, magnesium chloride, mannitol, potassium chloride, and sodium hydroxide in the approved indications remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAHs should continue to monitor cases of hepatic artery thrombosis in the context of the RMP and closely monitor cases of infections to determine the potential role of breaches in aseptic usage of the product. In addition the MAHs should monitor and adequately document off-label use in paediatrics.

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.

Applicant: various

PRAC Lead: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### **Background**

Spironolactone is a steroidal antimineralocorticoid indicated for the treatment of essential hypertension, congestive heart failure (alone or in combination with standard therapy), including New York Heart Association (NYHA) class III-IV severe heart failure to increase survival and reduce the risk of hospitalization when used in addition to standard therapy, conditions in which secondary hyperaldosteronism may be present, including liver cirrhosis accompanied by oedema and/or ascites, nephrotic syndrome, and other oedematous conditions (alone or in combination with standard therapy), short-term preoperative treatment of patients with primary hyperaldosteronism, diuretic-induced hypokalemia/hypomagnesaemia as adjunctive therapy, establishing a diagnosis of primary hyperaldosteronism, adjunctive therapy in diuretic-induced hypokalaemia/hypomagnesaemia, management of hirsutism.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing spironolactone, 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 spironolactone-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning on the concomitant use of medicinal products known to cause hyperkalaemia and to include in the interaction with other medicinal products and other forms of interaction section that concomitant use of trimethoprim/sulfamethoxazole may result in clinically relevant hyperkalaemia. In addition the product information should be updated to include bullous skin reaction, pemphigoid, as a new undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied<sup>27</sup>.
- The PRAC noted that there is a significant diversity between the reference safety information of various MAHs/medicinal products. In order to keep the product information of various spironolactone preparations up to date and aligned, the following topics should be reviewed by the relevant MAHs:
  - Severe/serious skin reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and/or drug reaction with eosinophilia and systemic symptoms (Sanofi, Teva, Riemser, Gedeon Richter, and Actavis).
  - Changes in the blood count (complete blood count; thrombocytopenia and/or leukopenia/agranulocytosis) (Teva and Actavis).

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<sup>27</sup> Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position



- Pfizer and Sanofi shall in the next PSUR discuss the topic of angioedema.

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. Trandolapril, verapamil (NAP) - PSUSA/03005/201503

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Applicant: various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

Trandolapril is an angiotensin-converting-enzyme inhibitor (ACE inhibitor) and verapamil is a calcium channel blocker. Trandolapril/verapamil is indicated for the treatment of essential hypertension in patients whose blood pressure has been normalized with the individual components at similar dosage, or in patients whose blood pressure is not adequately controlled on trandolapril or verapamil alone.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of nationally authorised medicines-containing trandolapril/verapamil, 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 trandolapril/verapamil-containing products in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to include a warning in the interaction with other medicinal products and other forms of interaction section on the interaction between dabigatran and verapamil when co-administered. Therefore the current terms of the marketing authorisation(s) should be varied<sup>28</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.

#### 6.4. Follow-up to PSUR/PSUSA procedures

##### 6.4.1. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBP), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – INFANRIX HEXA (CAP) - EMEA/H/C/000296/LEG 116

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Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

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<sup>28</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

Scope: Following the recommendation of the PSUR single assessment procedure adopted at PRAC in May 2015(PSUSA/00001122/201410), submission of additional information on the recently observed increase in the reported cases of regression of psychomotor development and a cumulative review of cases in relation with lack of reconstitution

## Background

Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBP), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) as a conjugate vaccine (adsorbed) is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b.

Following the evaluation of the most recently submitted PSURs for Infanrix Hexa (D-T-Pa-HBP-IPV-Hib conjugate vaccine (adsorbed)), the PRAC requested the MAH to submit further data on a recently observed increase in reported cases of regression of psychomotor development (see [PRAC minutes June 2015](#)). The responses were assessed by the Rapporteur for further PRAC advice.

## Summary of advice/conclusion(s)

- Based on the review of the data submitted by the MAH (including a discussion on the recent increase in reporting, the cumulative review of clinical trials and post-marketing cases, patient exposure, case definition/epidemiology, review of non-clinical data, potential biological mechanisms, and type of vaccination schedule), the PRAC agreed that the analysis of reported cases considered all available data and did not constitute a new safety issue, given the limitations of spontaneous reporting data quality. However, before concluding on the issue, the MAH should submit to EMA, within 60 days, further observed versus expected analyses.

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

### 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>29</sup>

See also Annex I. 16.1.

#### 7.1.1. Deferasirox – EXJADE (CAP) - EMEA/H/C/PSP/0010.4.A.1

Applicant: Novartis Europharm Ltd.

PRAC Rapporteur: Corinne Fechant

Scope: Evaluation of a revised PASS protocol for study C1CL670E2422: observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years

## Background

Deferasirox is an iron chelating agent indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major, for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in some specific sub-populations, as well as for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is

<sup>29</sup> In accordance with Article 107n of Directive 2001/83/EC

contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes under certain conditions.

The PRAC adopted the draft protocol for the PASS study CICL670E2422: an observational cohort study in paediatric non transfusion dependant-thalassaemia (NTDT) patients over 10 years, in January 2015. Following a request from the FDA to include patients taking a newly developed form of deferasirox (film-coated) not yet available in the EU market, the MAH submitted a substantial protocol amendment for this study to the PRAC.

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

The PRAC, having considered the revised protocol version 03 in accordance with Article 1070 of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s), as the Committee considered that the study design, including the population, the sample size, and milestones, should be resolved before the final protocol is approved.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 days-assessment timetable will be applied.

### **7.1.2. Hydroxyethyl starch (NAP) - EMEA/H/N/PSP/0024.1**

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Applicant: B. Braun Melsungen AG

PRAC Rapporteur: Qun-Ying Yue

Scope: Revised PASS protocol (drug utilisation study) to assess the effectiveness of the risk minimisation taken following the European Commission decision dated 19 December 2013 for the referral procedure EMEA/H/A-107i/1376

#### **Background**

For background, see [PRAC minutes July 2015](#). The Rapporteur assessed the draft revised protocol submitted in accordance with the agreed timetable.

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

The PRAC, having considered the joint draft protocol version 1.1\_24 in accordance with Article 107n of Directive 2001/83/EC, endorsed by consensus the protocol for PASS study for the above listed medicinal products.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>30</sup>**

See also Annex I. 16.2.

### **7.2.1. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/MEA/011.1**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

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<sup>30</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: MEA's responses to MEA 011 [revised synopsis protocol for a study to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer, representing real world evidence from relevant countries] as adopted in June 2015

## **Background**

Olaparib is a human poly (ADP-ribose) polymerase enzymes inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to platinum-based chemotherapy.

As part of the RMP for Lynparza, a centrally authorised medicine containing olaparib, the MAH was required to conduct a PASS study D0816R00008: a study to collect and/or retrieve prospective data from sizeable patient cohorts with ovarian cancer, representing real world evidence from relevant countries (category 3). The aim was to collect and/or retrieve prospective data from sizeable patient cohorts representing real world evidence from relevant countries, to further characterise the safety concern of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) in ovarian cancer patients. The MAH submitted a revised study synopsis for study D0816R00008 along with responses to the questions raised in the previous round of assessment, which were assessed by the Rapporteur. The PRAC was requested to provide advice to CHMP on the protocol submitted by the MAH.

## **Summary of advice**

- The synopsis for study D0816R00008 could be considered acceptable. All issues raised in the previous round of assessment are considered resolved. However the MAH should take into account some issues raised with regards to the inclusion criteria, exclusion criteria, the data sources and the questionnaires section, when submitting the final PASS protocol for review.

### **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>31</sup>**

None

### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>32</sup>**

See Annex I.16.4.

### **7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>33</sup>**

See Annex I.16.5.

### **7.6. Others**

None

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<sup>31</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>32</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>33</sup> In line with the revised variations regulation for any submission before 4 August 2013

## 7.7. New Scientific Advice

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

## 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.

### 8.3. Renewals of the marketing authorisation

#### 8.3.1. Apixaban – ELIQUIS (CAP) - EMEA/H/C/0002148/R/0034 (with RMP)

Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

#### Background

Apixiban is a factor Xa inhibitor indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults under certain conditions.

Eliquis, a centrally authorised medicine containing apixiban, was authorised in 2011.

The MAH submitted an application for the renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this five year-renewal with regard to safety and risk management aspects.

#### Summary of advice

- Based on the review of the available pharmacovigilance data for Eliquis and the CHMP Rapporteur's assessment report, the PRAC considered that an additional 5 year renewal is necessary. Further characterisation of the important risk of bleeding is warranted through the agreed ongoing study programmes as well as pharmacovigilance activities (particularly extension phase of the AVERROES<sup>34</sup> study (CV185048) and targeted bleeding questionnaire for reports of excessive bleeding events during the post marketing period. In addition, additional risk minimisation

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<sup>34</sup> Double-blind, double-dummy superiority trial. Apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment

measures have been implemented, for which the effectiveness will be evaluated in a PASS<sup>35</sup> study, its final report is anticipated for May 2017.

### 8.3.2. Retigabine – TROBALT (CAP) - EMEA/H/C/001245/R/0036 (with RMP)

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

**Action:** For adoption of advice to CHMP

#### **Background**

Retigabine is an antiepileptic indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.

Trobalt, a centrally authorised medicine containing retigabine, was authorised in 2011.

The MAH submitted an application for the renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this five year-renewal with regard to safety and risk management aspects.

#### **Summary of advice**

- Based on the review of the available pharmacovigilance data for Trobalt and the CHMP Rapporteur's assessment report, the PRAC considered that an additional 5 year renewal is necessary due to uncertainties relating to the risk of eye disorders, including pigment changes in the retina and a possibility of functional abnormalities associated with retinopathy including potentially severe visual impairment. The PRAC supported the proposed changes in the product information to reflect acute vitelliform maculopathy with a few amendments. In addition, the educational materials for HCPs should be updated to include information on the risk of vitelliform maculopathy and to ensure that dilated fundus photography and macular optical coherence tomography (OCT) imaging are included in the ophthalmological examinations conducted at treatment initiation and at least every 6 months thereafter while the treatment is ongoing. The target audience of the educational material was clarified (neurologists and ophthalmologists, and other HCPs according to national requirements). The PRAC agreed that there should be timely distribution of the revised material including a cover letter highlighting what has been updated in the new version.

## 9. Product related 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.

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<sup>35</sup> Evaluation of the effectiveness of Eliquis (apixaban) risk minimisation tools in European Economic Area (EEA) countries

## **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**

None

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

None

### **10.3. Other requests**

None

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

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

None

### **11.2. Other requests**

None

## **12. Organisational, regulatory and methodological matters**

### **12.1. Mandate and organisation of the PRAC**

#### **12.1.1. Using PRAC plenary time efficiently and effectively – follow-up from discussion at the Luxembourg PRAC strategic review and learning meeting**

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At the organisational matters teleconference on 19 November 2015, the EMA Secretariat presented a summary of the discussion held at the Luxembourg PRAC Strategic Review & Learning meeting on using PRAC plenary time efficiently and effectively, along with a proposed action plan which was endorsed by the PRAC.

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

### **12.2.1. CHMP guideline concerning tools for early access to medicines - accelerated assessment - revision**

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The EMA Secretariat presented to the PRAC a summary of the main comments received during the public consultation on the draft revised CHMP guidelines on tools for early access to medicines on accelerated assessment<sup>36</sup>. The comments from the public consultation will now be considered and an amended version of the revised CHMP guideline prepared. Once ready it will be presented to the CHMP, PRAC and CAT prior to finalisation.

### **12.2.2. CHMP guideline concerning tools for early access to medicines - conditional marketing authorisation - revision**

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The EMA Secretariat presented to the PRAC a summary of the main comments received during the public consultation on the draft revised CHMP guidelines on tools for early access to medicines on conditional marketing authorisation<sup>37</sup>. The amended draft revised CHMP guideline taking into account the comments received from the public consultation will be presented to the CHMP in November for final adoption.

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

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PRAC lead: Jolanta Gulbinovič; Amy Tanti

At the organisational matters teleconference on 19 November 2015, the EMA secretariat presented to PRAC an updated draft guideline on the conduct of pharmacovigilance for medicines used by the paediatric population, taking into consideration the written PRAC comments sought following the October 2015 PRAC meeting. Further discussion is planned at the December 2015 PRAC meeting.

### **12.2.4. Paediatric pharmacovigilance - organ maturation tables**

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The topic was deferred to the December 2015 PRAC meeting.

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

### **12.3.1. EMA workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants (DOAC) on 23 November 2015**

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PRAC lead: Jean-Michel Dogné; Rafe Suvarna

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<sup>36</sup> Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004

<sup>37</sup> Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004



The EMA Secretariat presented to the PRAC the final agenda ([EMA/681537/2015](#))<sup>38</sup> for the EMA workshop on the role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants taking place on 23 November 2015.

### 12.3.2. Scientific Advice Working Party (SAWP) – update on pilot for non-imposed PASS protocols

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The EMA Secretariat presented to the PRAC an update on the pilot involving the SAWP for advice on non-imposed non-interventional PASS protocols, including some procedural principles, an outline of the different roles of those participating in the pilot PASS protocols procedure particularly for the joint PRAC/SAWP delegate and alternate, and for the PRAC expert. The first two requests for advice received as part of the pilot were highlighted to the PRAC along with their respective procedural timetables. The PRAC raised some comments on the process and requested some clarifications on some aspects, and therefore it was agreed that an explanatory document will be prepared by EMA and circulated to the PRAC.

### 12.3.3. Working Party with Healthcare Professionals’ Organisations (HCPWP)- work plan 2016

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At the organisational matters teleconference on 19 November 2015, the PRAC endorsed the HCPWP work plan for 2016 and welcomed the opportunities for further dialogue and interaction with representatives of healthcare professionals, academia and learned societies, as described in the revised work plan.

### 12.3.4. Working Party with Patients’ and Consumers’ Organisations (PCWP) – work plan 2016

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At the organisational matters teleconference on 19 November 2015, the PRAC endorsed the PCWP work plan for 2016 and fully endorsed the value of the strengthened involvement of patient and consumer organisations in a wide array of EMA activities, including PRAC activities where appropriate.

## 12.4. Cooperation within the EU regulatory network

None

## 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

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<sup>38</sup> See also background document ([EMA/746962/2015](#))

## **12.7. PRAC work plan**

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

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At the organisational matters teleconference on 19 November 2015, the EMA Secretariat presented to the PRAC a short update on the development of the draft 2016 PRAC work plan. PRAC members welcomed the progress made and offered ongoing support in this important exercise.

## **12.8. Planning and reporting**

None

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

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

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

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

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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.

### **12.10.2. Periodic Safety Update Reports Single Assessment (PSUSA) – proactive publication of PRAC assessment reports for nationally approved products (NAPs)**

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The EMA Secretariat presented to the PRAC a proposal to publish the PRAC assessment reports (sections 1-4) for PSUR single assessment (PSUSA) procedures involving nationally approved products (NAPs), and for all regulatory outcomes. The aim is to facilitate availability of PSUSA outcomes to all MAHs in particular for NAPs not involved in the procedure. The proposal includes the creation of a drafting group involving PRAC and CMDh members. The intention is to have the initiative adopted by PRAC and CMDh by Q4 2016.

### **12.10.3. PSURs repository**

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None

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

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The PRAC endorsed the draft revised EURD list version November 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 November 2015, the updated EURD list was adopted by the CHMP and CMDh at their November 2015 meeting and published on the EMA website on 27/11/2015, 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

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PRAC lead: Sabine Straus

At the organisational matters teleconference on 19 November 2015, the PRAC was updated on the outcome of the November 2015 SMART Working Group (SMART WG) work stream (WS) 1. As a follow-up to the October 2015 discussion, the SMART WG further discussed the important medical events (IME) and the designated medical events (DLE) lists and gave its consideration regarding transparency aspects, aiming at publishing these lists in the future. In addition, the SMART WG was updated on the progress made within the 'Strengthening Collaborations for Operating Pharmacovigilance in Europe' ([SCOPE](#)) project. Finally, the SMART WG WS1 was updated on an analysis regarding the compliance with PRAC recommendations for variations in relation to signals for CAPs.

In addition, the PRAC was updated on the SMART WG WS 2-3 main activities. In October 2015, the WS 2-3 discussed in particular the final draft guideline on screening for adverse drug reactions in EudraVigilance (so called methodological and statistical guidance) as well as the results from the final survey concerning the new electronic reaction monitoring reports (eRMR) pilot format.

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

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

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None

#### 12.12.2. Additional monitoring

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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 24/11/2015 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#))

## **12.13. EudraVigilance database**

### 12.13.1. Activities related to the confirmation of full functionality - EudraVigilance auditable requirement communication plan

The EMA Secretariat presented to the PRAC the draft communication plan linked to the EudraVigilance requirements project, intended for national competent authorities, MAHs and sponsors of clinical trials. This draft communication plan, currently under consultation by different bodies including the PRAC, is planned for publication by end of Q1 2016. PRAC delegates were invited to provide written comments by 11 November 2015.

### 12.13.2. EudraVigilance Access Policy – technical implementation

The EMA Secretariat presented to the PRAC as a follow-up from the October 2015 PRAC meeting (see [PRAC minutes October 2015](#)) previews of how the revised EudraVigilance Access Policy will be implemented (when available). The PRAC was reminded that the revised policy is planned for adoption by the EMA Management Board in December 2015 ([EMA/MB/169416/2015 Version 4](#)) before coming into force.

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

### 12.14.1. Risk management systems

None

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

None

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

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

None

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

None

## **12.16. Community procedures**

### **12.16.1. Referral procedures for safety reasons**

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None

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

### **12.17.1. Conditional renewals and annual re-assessments - revision of assessment report templates**

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PRAC lead: Ulla Wändel-Liminga; Dolores Montero Corominas

The EMA Secretariat presented to the PRAC a proposal for revised assessment report templates for conditional renewals and annual re-assessments, following the same principles as the revised process for five-year renewals. The revised assessment report templates for conditional renewals and annual re-assessments are planned to be implemented for procedures starting in January 2016. PRAC delegates were invited to provide written comments by 25 November 2015.

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

### **12.18.1. Public participation in pharmacovigilance**

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None

### **12.18.2. Safety communication - PRAC meeting highlights**

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PRAC lead: Jane Ahlqvist-Rastad

At the organisational matters teleconference on 19 November 2015, a proposal for topics to be included in the PRAC highlights was presented to the PRAC, i.e. in addition to inclusion of the initiation and conclusion of referrals, with the links to related documents and PRAC agenda as standard. The PRAC was reminded of the current approach with regard to inclusion of topics in the PRAC highlights. The new proposal is to systematically include in the PRAC highlights, in addition to information on referrals, information on other selected procedures. The PRAC endorsed the new proposal in principle and it was agreed to aim for starting with the revised approach in Q1 2016, subject to prior consultation with officials responsible for communication activities in the Member States.

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Rapid Alert/Non-Urgent Information (RA/NUI) – templates update**

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At the organisational matters teleconference on 19 November 2015, the EMA Secretariat presented to the PRAC a proposal to revise the rapid alert and non-urgent information templates with the aim of simplifying and harmonising both templates. The main proposed changes were highlighted to the PRAC. These revised templates will be implemented in 2016 as part of a future release of the European Pharmacovigilance Issues Tracking Tool (EPITT) database.

## **12.20. Others**

None

## **13. Any other business**

### **13.1. Strategy on impact of pharmacovigilance**

At the organisational matters teleconference on 19 November 2015, the EMA Secretariat presented to the PRAC a revised draft of the PRAC strategy paper on measuring the impact of Pharmacovigilance activities and work plan following a workshop that took place in September 2015. A follow-up discussion and final adoption of the strategy paper and work plan is planned in December 2015.

## 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

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Generic

Scope: Treatment of essential hypertension

#### 14.1.2. Betulae cortex dry extract - EMEA/H/C/003938

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Scope: Treatment of partial thickness wounds

#### 14.1.3. Brivaracetam - EMEA/H/C/003898

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Scope: Treatment of partial-onset seizures

#### 14.1.4. Elotuzumab - EMEA/H/C/003967, Orphan

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Applicant: Bristol-Myers Squibb

Scope: Treatment of myeloma

#### 14.1.5. Etanercept - EMEA/H/C/004007

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Scope: Treatment of arthritis

#### 14.1.6. Ferric maltol - EMEA/H/C/002733

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Scope: Treatment of iron deficiency anaemia

#### 14.1.7. Mercaptamine - EMEA/H/C/004038, Orphan

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Applicant: Lucane Pharma

Scope: Treatment of corneal cystine deposits

#### 14.1.8. Mercaptamine - EMEA/H/C/003769, Orphan

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Applicant: Orphan Europe S.A.R.L.

Scope: Treatment of corneal cystine deposits

#### [14.1.9. Necitumumab - EMEA/H/C/003886](#)

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Scope: Treatment of squamous non-small cell lung cancer

#### [14.1.10. Opicapone - EMEA/H/C/002790](#)

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Scope: Treatment of Parkinson's disease and motor fluctuations

#### [14.1.11. Pegaspargase - EMEA/H/C/003789](#)

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Scope: Combination therapy in acute lymphoblastic leukaemia (ALL)

#### [14.1.12. Pemetrexed - EMEA/H/C/004072](#)

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Generic

Scope: Treatment of unresectable malignant pleural mesothelioma

#### [14.1.13. Pitolisant - EMEA/H/C/002616, Orphan](#)

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Applicant: Bioprojet Pharma

Scope: Treatment of narcolepsy

#### [14.1.14. Recombinant L-asparaginase - EMEA/H/C/002661, Orphan](#)

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Applicant: Medac Gesellschaft fuer klinische Spezialpraeparate mbH

Scope: Combination therapy for B/T cell lymphoblastic leukaemia (ALL) or B/T cell lymphoblastic lymphoma (LBL)

### **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 these updated versions of the RMP for the below mentioned medicines.

#### [14.2.1. Tenofovir disoproxil – VIREAD \(CAP\) - EMEA/H/C/000419/II/0154/G](#)

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Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope: Update of the RMP to remove the pharmacokinetic (PK) sub-study of the category 3 study GSUS-174-0144. Update of the RMP to change the agreed due date of the category 3 study GS-US-236-0103. Update of the RMP to update in Part II the Antiretroviral Pregnancy Registry exposure in line with EMA request. Update of the RMP to reflect the milestones for category 3 studies GS-US-174-0115 and GS-US-174-0144 in line with those already agreed in the PIP. In addition, the MAH took the opportunity of this procedure to update studies and exposure data as well as update status/milestones of several studies. The updated RMP version 19 is provided

#### [14.2.2. Zoledronic acid – ACLASTA \(CAP\) - EMEA/H/C/000595/II/0056](#)

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Ulla Wändel Liminga



Scope: Update of the RMP (version 11.0) in order to introduce a patient reminder card as an additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw and to propose indicators to measure the effectiveness of this new measure

#### **14.2.3. Zoledronic acid – ZOMETA (CAP) - EMEA/H/C/000336/II/0069**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP to reflect the PSUR data approved in procedure EMEA/H/C/PSUSA/00003149/201408 and to include an additional new minimisation measure (introduction of the reminder card in osteonecrosis of the jaw (ONJ)) as well as to propose indicators to measure its effectiveness. The MAH also took the opportunity to add the targeted follow-up checklist for the identified risk hypocalcaemia in the RMP

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

#### **14.3.1. Ambrisentan – VOLIBRIS (CAP) - EMEA/H/C/000839/II/0039**

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Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of section 4.4 of the SmPC in relation to the current recommendations for liver function and section 5.1 of the SmPC with data on aminotransferase abnormalities from an analysis of the clinical study report (CSR) for PASS 'AMB110094 (VOLT)'. The current 'healthcare professional information' in Annex II has been updated accordingly as well as the Package Leaflet and RMP (version 6)

#### **14.3.2. Bivalirudin – ANGIOX (CAP) - EMEA/H/C/000562/II/0062**

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Applicant: The Medicines Company UK Ltd.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.2 and 4.4 of the SmPC in order to update posology instructions and update warning of use of bivalirudin in case of haemorrhage. The Package Leaflet is updated accordingly

#### **14.3.3. Bromfenac – YELLOX (CAP) - EMEA/H/C/000098/R/0014**

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Applicant: PharmaSwiss Ceska Republika s.r.o

PRAC Rapporteur: Torbjorn Callreus

Scope: Evaluation of an RMP in the context of a 5-year renewal of the marketing authorisation

#### **14.3.4. Daclatasvir – DAKLINZA (CAP) - EMEA/H/C/003768/II/0010/G**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Margarida Guimarães

Scope: Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 in order to update the safety information based on final results of clinical study AI444216 (ALLY-2): 'phase 3 evaluation of daclatasvir plus sofosbuvir in treatment-naïve and treatment experienced chronic

hepatitis C (genotype 1, 2, 3, 4, 5, or 6) subjects coinfecting with human immunodeficiency virus (HIV)'. The Package Leaflet is updated accordingly. In addition, update of sections 4.2, 4.4, 4.8, 5.1, 5.2 in order to update the safety information based on the final results of clinical study AI444215 (ALLY-1): 'phase 3 evaluation of daclatasvir, sofosbuvir, and ribavirin in genotype 1-6 chronic hepatitis C infection subjects with cirrhosis who may require future liver transplant and subjects post-liver transplant'. The Package Leaflet is updated accordingly

#### 14.3.5. Denosumab – XGEVA (CAP) - EMEA/H/C/002173/II/0041

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC regarding the risk of off-treatment hypercalcaemia following cessation of Xgeva treatment in young patients with growing skeletons. The Package Leaflet is updated accordingly. The RMP (version 15.0) is updated accordingly

#### 14.3.6. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP) - EMEA/H/C/002702/WS/0789; HEXAXIM (Art 58<sup>39</sup>) - EMEA/H/W/002495/WS/0789; HEXYON (CAP) - EMEA/H/C/002796/WS/0789

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Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.8 of the SmPC, upon request by PRAC following the assessment of PSUSA/10091/201410, to include the adverse drug reactions (ADRs) 'convulsion with or without fever' and 'anaphylactic reaction'. The Package Leaflet has been updated accordingly. The RMP (version 10.0) is updated accordingly

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

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Dolores Montero Corominas

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

#### 14.3.8. Eribulin – HALAVEN (CAP) - EMEA/H/C/002084/II/0028

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Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include a new indication for Halaven 0.44 mg/ml solution for injection to expand its use to the treatment of soft tissue sarcoma, following the outcome of a Phase 3 study, Study 309. As a consequence, sections 4.1, 4.4, 4.8, and 5.1

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<sup>39</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)

of the SmPC are updated in order to update the safety information. The Package Leaflet and RMP are updated accordingly

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

Applicant: Bial - Portela & C<sup>a</sup>, S.A.

PRAC Rapporteur: Martin Huber

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

#### 14.3.10. Everolimus – AFINITOR (CAP) - EMEA/H/C/001038/II/0048

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Extension of indication to include a new indication for the treatment of unresectable or metastatic, well-differentiated non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease for Afinitor. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance

#### 14.3.11. Everolimus – VOTUBIA (CAP) - EMEA/H/C/002311/II/0039

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Martin Huber

Scope: Update of section 4.8 (for dispersible tablets) and section 4.8 and 5.2 (for tablets) of the SmPC in order to update the safety and efficacy information with the data from the final clinical study report (CSR) comprising the extension phase of study M2302 in fulfilment of PAM (ANX 027). The Annex II and Package Leaflet are updated accordingly. In addition, the MAH updated section 4.2 and 4.4 of the SmPC in order to align with Afinitor SmPC. Moreover, the RMP (version 11.0) is updated accordingly

#### 14.3.12. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0065/G

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on review of all available safety data. The Package Leaflet and RMP are updated accordingly. Additionally, the due date for a category 3 study in the RMP is proposed to be updated

#### 14.3.13. Golimumab – SIMPONI (CAP) - EMEA/H/C/000992/II/0063

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the SmPC sections 4.2 and 5.1 in order to reflect the data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic

arthritis (pJIA). The Package leaflet is proposed to be updated accordingly. The RMP is updated accordingly

#### **14.3.14. Human coagulation factor VIII, human von Willebrand factor – VONCENTO (CAP) - EMEA/H/C/002493/II/0017/G**

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Applicant: CSL Behring GmbH

PRAC Rapporteur: Sabine Straus

Scope: Update of section 4.8 of the SmPC in order to update the frequencies of undesirable effects to reflect the final clinical study data from study CSLCT-BIO-08-53 in haemophilia A paediatric patients. The Package Leaflet is updated accordingly. The submission of the final clinical study report (CSR) CSLCT-BIO-08-53 also leads to changes to the RMP (version 6.1) in order to update the company core safety information (CCSI). In addition, submission of a revised RMP in order to remove the commitment to conduct a post-marketing study for haemophilia A patients (CSLCT-BIO-12-78) for Voncento as consequence of new data from study CSLCT-BIO-08-53

#### **14.3.15. Human fibrinogen, human thrombin – EVICEL (CAP) - EMEA/H/C/000898/II/0032**

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Applicant: Omrix Biopharmaceuticals N. V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the SmPC sections 4.2 and 5.1 in order to reflect data from a multicentre, placebo-controlled, double-blind, randomised-withdrawal, parallel group study (GO KIDS) in children (2 to 17 years of age) with active polyarticular juvenile idiopathic arthritis (pJIA). The Package leaflet is proposed to be updated accordingly. The RMP is updated accordingly

#### **14.3.16. Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – CERVARIX (CAP) - EMEA/H/C/000721/II/0067**

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Applicant: GlaxoSmithKline Biologicals

PRAC Rapporteur: Jean-Michel Dogné

Scope: Extension of indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP (version 11.0) is updated accordingly

#### **14.3.17. Human rotavirus, live attenuated – ROTARIX (CAP) - EMEA/H/C/000639/II/0078**

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Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Jean-Michel Dogné

#### **14.3.18. Ibrutinib – IMBRUVICA (CAP) - EMEA/H/C/003791/II/0013**

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope: Update of SmPC sections 4.8 and 4.9 with information on hepatic failure and hepatotoxicity. The Package Leaflet and RMP are updated accordingly

#### 14.3.19. Liraglutide – SAXENDA (CAP) - EMEA/H/C/003780/II/0006

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Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Submission of the final report on the assessment of breast cancer cases found in trial NN8022-1839 (Phase 3a clinical trial). This fulfils MEA 004 listed in the RMP as an additional category 3 pharmacovigilance study. The results of the study do not require an update of the product information

#### 14.3.20. Meningococcal group a, c, w135 and y conjugate vaccine – MENVEO (CAP) - EMEA/H/C/001095/II/0056

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.8 of the SmPC in order to add 'facial paresis' as an adverse drug reaction and to provide further safety information based on the final clinical study report (CSR) of study V59\_340B in order to fulfil the post-authorisation measure (MEA 023). The Package Leaflet is updated accordingly. Moreover, the RMP (version 8.2) is updated accordingly

#### 14.3.21. Nivolumab – NIVOLUMAB BMS (CAP) - EMEA/H/C/003840/II/0001

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 4.4 and 4.8 of the SmPC to include safety information regarding the adverse drug reactions (ADR) toxic epidermal necrolysis (TEN) and encephalitis. The Package Leaflet and the RMP (version 1.3) are updated accordingly

#### 14.3.22. Olaparib – LYNPARZA (CAP) - EMEA/H/C/003726/II/0001/G

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Applicant: AstraZeneca AB

PRAC Rapporteur: Carmela Macchiarulo

Scope: Update of sections 4.4, 4.5 and 4.6 of the SmPC in order to include further information related to pharmacokinetic interactions based on the in vivo interaction study D0816C00008, 3 in vitro interaction studies (ADME-AZS-Wave3-140714, ADME-AZS-Wave3-140725 and 140483) and data from previously submitted interaction studies. The provision of the final clinical study report (CSR) of study D0816C00008 addresses the post-authorisation measure MEA 004. Furthermore, the MAH provided the study report of in vitro study 8305083 as part of the application. In addition, the MAH took the opportunity to add the published ATC code in section 5.1 of the SmPC, and to implement minor editorial changes in the SmPC, labelling and Package Leaflet. A revised RMP (version 6) was provided as part of the application, which includes consequential changes related to data on interactions. Further, the MAH is taking the opportunity to update the due dates for the provision of the final study reports of the category 3 studies D0816C00005 and D0816C00006, and to add the new category 3 study D0816C00010

#### 14.3.23. Pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/II/0002

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Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Sabine Straus

Scope: Update of sections 4.8, 5.1 and 5.2 of the SmPC with safety and pharmacokinetic (PK) data based on the clinical study report (CSR) of study P006v01. Further, the adverse drug reaction (ADR) Guillain-Barré syndrome (GBS) has been added to sections 4.4 and 4.8 of the SmPC. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to revise the text referring to fatal cases of pneumonitis in section 4.4 of the SmPC, to implement minor editorial changes in the annexes. The RMP (version 2.0) is updated accordingly

#### 14.3.24. Perampanel – FYCOMPA (CAP) - EMEA/H/C/002434/II/0023

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.5 and 5.2 in order to update the safety information based on the results of a mass balance study

#### 14.3.25. Pyronaridine – PYRAMAX (Art 58) - EMEA/H/W/002319/II/0002

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Isabelle Robine

Scope: Update of SmPC section 4.1 to remove restrictions on repeated course of treatment in any individual and use only in areas of low transmission with evidence of artesmisinin resistance, based on further clinical experience. Consequent changes in SmPC sections 4.2, 4.4, 4.8 and the Package Leaflet are also included. A recommended change is made to SmPC Section 4.2 in relation to dosing in mild to moderate renal impairment

#### 14.3.26. Pyronaridine – PYRAMAX (Art 58) - EMEA/H/W/002319/X/0008/G

Applicant: Shin Poong Pharmaceutical Co., Ltd.

PRAC Rapporteur: Isabelle Robine

Scope: Line extension to add a new paediatric formulation 60 mg/20 mg granules for oral suspension. The product information for the 180 mg/60 mg film coated tablets has also been updated with data submitted for the line extension

#### 14.3.27. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP) - EMEA/H/C/000674/R/0096

Applicant: Sanofi Pasteur MSD SNC

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of an RMP in the context of a 5-year renewal of the marketing authorisation

#### 14.3.28. Teduglutide – REVESTIVE (CAP) - EMEA/H/C/002345/II/0020

Applicant: NPS Pharma Holdings Limited

PRAC Rapporteur: Torbjorn Callreus

Scope: Extension of indication to include paediatric population. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated in order to update the safety information. The Package Leaflet is updated accordingly

#### 14.3.29. Ticagrelor – BRILIQUE (CAP) - EMEA/H/C/001241/X/0029/G

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Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Line extension for a new strength of 60 mg with a new indication relating to history of myocardial infarction. Further, update of the product information of the existing 90 mg presentation with important clinical information from the PEGASUS study

### 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 favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR procedure(s).

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

##### 15.1.1. Abiraterone – ZYTIGA (CAP) - PSUSA/00015/201504

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

##### 15.1.2. Alipogene tiparvovec – GLYBERA (CAP) - PSUSA/10056/201504

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Applicant: uniQure biopharma B.V.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

##### 15.1.3. Alogliptin – VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone – INCRESYNC (CAP) - PSUSA/10061/201504

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

##### 15.1.4. Bazedoxifene, estrogens conjugated – DUAVIVE (CAP) - PSUSA/10321/201504

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.5. Budesonide, formoterol fumarate dihydrate – BIRESP SPIROMAX (CAP), BUDESONIDE/FORMOTEROL TEVA (CAP), BUDESONIDE/FORMOTEROL TEVA PHARMA B.V. (CAP), DUORESP SPIROMAX (CAP), VYLAER SPIROMAX (CAP) - PSUSA/10202/201504**

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Applicant: Teva Pharma B.V.

PRAC Rapporteur: Torbjorn Callreus

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.6. Cabozantinib – COMETRIQ (CAP) - PSUSA/10180/201503**

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Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.7. Catumaxomab – REMOVAB (CAP) - PSUSA/00581/201504**

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Applicant: Neovii Biotech GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.8. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins – CHONDROCELECT (CAP) - PSUSA/00273/201504**

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Applicant: TiGenix NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.9. Conestat alfa – RUCONEST (CAP) - PSUSA/00873/201504**

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Applicant: Pharming Group N.V

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.10. Defibrotide – DEFITELIO (CAP) - PSUSA/10086/201504**

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Applicant: Gentium S.p.A.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.11. Delamanid – DELTYBA (CAP) - PSUSA/10213/201504**

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Applicant: Otsuka Novel Products GmbH



PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.12. Dihydroartemisinin, piperazine tetraphosphate – EURARTESIM (CAP) - PSUSA/01069/201504**

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

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.13. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP), HEXAXIM (Art 58), HEXYON (CAP) - PSUSA/10091/201504**

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Applicant: Sanofi Pasteur

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.14. Empagliflozin – JARDIANCE (CAP) - PSUSA/10219/201504**

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.15. Febuxostat – ADENURIC (CAP) - PSUSA/01353/201504**

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Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Jan Neuhauser

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.16. Fenofibrate, pravastatin – PRAVAFENIX (CAP) - PSUSA/01363/201504**

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Applicant: Laboratoires SMB S.A.

PRAC Rapporteur: Corinne Fechant

Scope of procedure: Evaluation of a PSUSA procedure

**15.1.17. Florbetapir (<sup>18</sup>F) – AMYVID (CAP) - PSUSA/10032/201504**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Valerie Strassmann

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.18. Flutemetamol (<sup>18</sup>F) – VIZAMYL (CAP) - PSUSA/10293/201504

Applicant: GE Healthcare Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.19. Granisetron – SANCUSO (CAP) - PSUSA/10101/201504

Applicant: ProStrakan Limited

PRAC Rapporteur: Jolanta Gulbinovic

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.20. Histamine – CEPLENE (CAP) - PSUSA/01610/201504

Applicant: Meda AB

PRAC Rapporteur: Almath Spooner

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.21. Ibrutinib – IMBRUVICA (CAP) - PSUSA/10301/201504

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.22. Influenza vaccine (split virion, inactivated) – IDFLU (CAP), INTANZA (CAP) - PSUSA/01743/201504

Applicant: Sanofi Pasteur

PRAC Rapporteur: Miguel-Angel Macia

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.23. Insulin glulisine – APIDRA (CAP) - PSUSA/01752/201504

Applicant: Sanofi-aventis Deutschland GmbH

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.24. Ivabradine – CORLENTOR (CAP), PROCORALAN (CAP) - PSUSA/01799/201504

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Menno van der Elst

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.25. Laronidase – ALDURAZYME (CAP) - PSUSA/01830/201504

Applicant: Genzyme Europe BV

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.26. Ledipasvir, sofosbuvir – HARVONI (CAP) - PSUSA/10306/201504

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Margarida Guimarães

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.27. Macitentan – OPSUMIT (CAP) - PSUSA/10115/201504

Applicant: Actelion Registration Ltd.

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.28. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP) - PSUSA/10044/201504

Applicant: GlaxoSmithKline Biologicals S.A.

PRAC Rapporteur: Rafe Suvarna

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.29. Obinutuzumab – GAZYVARO (CAP) - PSUSA/10279/201504

Applicant: Roche Registration Ltd

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.30. Ocriplasmin – JETREA (CAP) - PSUSA/10122/201504

Applicant: ThromboGenics NV

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.31. Ofatumumab – ARZERRA (CAP) - PSUSA/02202/201504

Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Doris Stenver

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.32. Para-aminosalicylic acid – GRANUPAS (CAP) - PSUSA/10171/201504

Applicant: Lucane Pharma

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.33. Propranolol – HEMANGIOL (CAP) - PSUSA/10250/201504

Applicant: Pierre Fabre Dermatologie

PRAC Rapporteur: Dolores Montero Corominas

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.34. Ramucirumab – CYRAMZA (CAP) - PSUSA/10323/201504

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.35. Regadenoson – RAPISCAN (CAP) - PSUSA/02616/201504

Applicant: Rapidscan Pharma Solutions EU Ltd.

PRAC Rapporteur: Julie Williams

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.36. Siltuximab – SYLVANT (CAP) - PSUSA/10254/201504

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.37. Tocilizumab – ROACTEMRA (CAP) - PSUSA/02980/201504

Applicant: Roche Registration Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.38. Turoctocog alfa – NOVOEIGHT (CAP) - PSUSA/10138/201504

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.39. Umeclidinium bromide – INCRUSE (CAP) - PSUSA/10263/201504

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.1.40. Yttrium (<sup>90</sup>Y) chloride – YTRACIS (CAP), YTTRIGA (CAP) - PSUSA/03137/201503

Applicant: Cis Bio International

PRAC Rapporteur: Sabine Straus

Scope of procedure: Evaluation of a PSUSA procedure

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

#### 15.2.1. Telmisartan - MICARDIS (CAP), KINZALMONO (CAP), PRITOR (CAP), NAP hydrochlorothiazide, telmisartan – KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP) - PSUSA/02882/201504

Applicant: Bayer Pharma AG

PRAC Rapporteur: Carmela Macchiarulo

Scope of procedure: Evaluation of a PSUSA procedure

#### 15.2.2. Tenofovir – VIREAD (CAP), NAP - PSUSA/02892/201503

Applicant: Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine

Scope of procedure: Evaluation of a PSUSA procedure

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

#### 15.3.1. Dobutamine (NAP) - PSUSA/01151/201503

Applicant: various

PRAC Lead: Corinne Fechant

Scope: Evaluation of a PSUSA procedure

#### 15.3.2. Latanoprost (paediatric indication) (NAP) - PSUSA/01834/201504

Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

### 15.3.3. Nitrazepam (NAP) - PSUSA/02170/201503

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Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

### 15.3.4. Pimecrolimus (NAP) - PSUSA/02411/201503

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Applicant: various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

### 15.3.5. Triamcinolone (intraocular formulations) (NAP) - PSUSA/10292/201503

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Applicant: various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

## 16. ANNEX I – Post-authorisation safety studies (PASS)

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

### 16.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>40</sup>

#### 16.1.1. Tolvaptan – JINARC (CAP) - EMEA/H/C/PSP/0028.1

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Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Revised PASS protocol for a prospective study of the safety of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD) patients with an additional retrospective component to assess for risks associated with long term use

### 16.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>41</sup>

#### 16.2.1. Alemtuzumab – LEMTRADA (CAP) - EMEA/H/C/003718/MEA/005

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Applicant: Genzyme Therapeutics Ltd

PRAC Rapporteur: Torbjorn Callreus

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<sup>40</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>41</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: Protocol for a knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe alemtuzumab

#### **16.2.2. Insulin lispro – HUMALOG (CAP) - EMEA/H/C/000088/MEA/025.2; LIPROLOG (CAP) - EMEA/H/C/000393/MEA/018.2**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Julie Williams

Scope: Evaluation of MAH's responses to a request for supplementary information for MEA 025.1 [protocol synopsis for PASS study examining the effectiveness of risk minimisation on 200 units strength] as adopted in June 2015

#### **16.2.3. Interferon beta-1a – AVONEX (CAP) - EMEA/H/C/000102/MEA/084.3**

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Applicant: Biogen Idec

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's responses to REC 084.2 [PASS protocol] following the adoption of a request for supplementary information (RSI) as adopted in May 2015: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries

#### **16.2.4. Interferon beta-1a – REBIF (CAP) - EMEA/H/C/000136/MEA/039.3**

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Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: MAH's response to MEA 039.2 [PASS protocol] following the adoption of a request for supplementary information (RSI) as adopted in May 2015: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries

#### **16.2.5. Interferon beta-1b – BETAFERON (CAP) - EMEA/H/C/000081/MEA/021.3**

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Applicant: Bayer Pharma AG

PRAC Rapporteur: Julie Williams

Scope: MAH's response to REC 021.2 [PASS protocol] following the adoption of a request for supplementary information (RSI) as adopted in May 2015: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries

#### **16.2.6. Interferon beta-1b – EXTAVIA (CAP) - EMEA/H/C/000933/MEA/019.3**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Julie Williams

Scope: MAH's responses to MEA 019.2 [PASS potocol] RSI as adopted in May 2015: pregnancy outcomes in multiple sclerosis populations exposed and unexposed to interferon-beta – a register-based study in the Nordic countries

#### 16.2.7. Linaclotide – CONSTELLA (CAP) - EMEA/H/C/002490/MEA/009.2

Applicant: Almirall S.A

PRAC Rapporteur: Valerie Strassmann

Scope: MAH's responses to MEA 009.1 [revised protocol for linaclotide safety study for the assessment of diarrhoea - complications and associated risk factors in selected European populations with irritable bowel syndrome with constipation (IBS-C)] as adopted in July 2015

#### 16.2.8. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/002.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: MAH's responses to MEA 002 [revised protocol for naloxegol post-market observational drug utilisation study (study D2288R00081)] as adopted in May 2015

#### 16.2.9. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/004.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: MAH's responses to MEA 004 [revised protocol for naloxegol observational safety study in patients taking opioids for cancer pain (study D2288R00082)] as adopted in May 2015

#### 16.2.10. Naloxegol – MOVENTIG (CAP) - EMEA/H/C/002810/MEA/006.1

Applicant: AstraZeneca AB

PRAC Rapporteur: Almath Spooner

Scope: MAH's responses to MEA 006 [revised protocol for naloxegol observational safety study in patients taking opioids for non-cancer pain (study D2288R00084)] as adopted in May 2015

#### 16.2.11. Naltrexone, bupropion – MYSIMBA (CAP) - EMEA/H/C/003687/MEA 003

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Drug utilisation study (DUS): PASS protocol for a retrospective chart review and nested naltrexone/bupropion (NB) prescribing physician cross sectional survey

#### 16.2.12. Naltrexone, bupropion – MYSIMBA (CAP) - EMEA/H/C/003687/MEA 004

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: PASS protocol for the naltrexone/bupropion observational database study



16.2.13. Nivolumab – NIVOLUMAB BMS (CAP) - EMEA/H/C/003840/MEA/007; OPDIVO (CAP) - EMEA/H/C/003985/MEA/008

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for study CA209234, a non-interventional category 3 PASS: pattern of use, safety, and effectiveness of nivolumab in routine oncology practice

**16.3. Results of PASS imposed in the marketing authorisation(s)<sup>42</sup>**

None

**16.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>43</sup>**

16.4.1. Dexmedetomidine – DEXDOR (CAP) - EMEA/H/C/002268/II/0014 (without RMP)

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Applicant: Orion Corporation

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report of DexDUS (study 3005021): a multinational, observational study to investigate the use of dexmedetomidine (Dexdor) in clinical practice with a focus to characterise the use in the paediatric population

16.4.2. Fondaparinux sodium – ARIXTRA (CAP) - EMEA/H/C/000403/II/0067 (with RMP)

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Applicant: Aspen Pharma Trading Limited

PRAC Rapporteur: Qun-Ying Yue

Scope: Submission of the final study report for WE115280: Physician adherence to fondaparinux prescribing information for patients with superficial vein thrombosis (SVT) of the lower limbs. There is no change to the product information based on the outcome and conclusions of this study

16.4.3. Memantine – AXURA (CAP) - EMEA/H/C/000378/WS/0804; EBIXA (CAP) - EMEA/H/C/000463/WS/0804; MEMANTINE MERZ (CAP) - EMEA/H/C/002711/WS/0804 (with RMP)

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Applicant: Merz Pharmaceuticals GmbH, H. Lundbeck A/S

PRAC Rapporteur: Dolores Montero Corominas

Scope: Submission of the final results of a non-interventional PASS to examine the use of memantine and risk of prostate cancer (nationwide case-control studies in Denmark and Sweden) in order to fulfil MEA 31.5. The RMP (version 8.0) has been updated: 1) to delete the important potential risk 'prostate cancer' based on the results of case control studies, 2) to delete the important identified risk 'overdose with pump device' based on the PSUR 16 PRAC AR and 3) to update clinical trial exposure and post-authorization experience

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<sup>42</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>43</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

#### 16.4.4. Panitumumab – VECTIBIX (CAP) - EMEA/H/C/000741/II/0071 (with RMP)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Julie Williams

Scope: Submission of the final study report study 20101121 (category 3): study to measure the effectiveness of the risk minimisation measures. A revised RMP (version 17) has been provided to reflect the results of the study, as well as general updates of clinical / post-marketing data in line with a new DLP and current product information

#### 16.4.5. Tenofovir disoproxil – VIREAD (CAP) - EMEA/H/C/000419/WS0731/0147 (with RMP)

tenofovir disoproxil, emtricitabine – EVIPLERA (CAP) -

EMEA/H/C/002312/WS0731/0056; TRUVADA (CAP) -

EMEA/H/C/000594/WS0731/0113 - (with RMP)

tenofovir disoproxil, emtricitabine, efavirenz – ATRIPLA (CAP) -

EMEA/H/C/000797/WS0731/0101 (with RMP)

tenofovir disoproxil, emtricitabine, elvitegravir, cobicistat – STRIBILD (CAP) -

EMEA/H/C/002574/WS0731/0044 (with RMP)

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Applicant: Bristol-Myers Squibb and Gilead Sciences International Ltd

PRAC Rapporteur: Isabelle Robine (Viread); Julie Williams (Truvada), Martin Huber (Atripla), Menno van der Elst (Eviplera), Rafe Suvarna (Stribild)

Scope: Submission of the final clinical study report for Viread study GS-US-104-0423 'phase 4 cross-sectional study of bone mineral density in human immunodeficiency virus (HIV)-1 infected subjects' in fulfilment of a post-authorisation measure (PAM) for Viread, Truvada, Eviplera, Stribild and Atripla (category 3 additional pharmacovigilance activity for Viread, Truvada, Eviplera and Stribild, and category 4 for Atripla). The RMP for each product is updated accordingly

### 16.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation<sup>44</sup>

#### 16.5.1. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 046.5

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Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Sixth year interim report from a registry in juvenile idiopathic arthritis (JIA) patients

#### 16.5.2. Adalimumab – HUMIRA (CAP) - EMEA/H/C/000481/MEA 075.4

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Applicant: AbbVie Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Third annual progress report for a long-term non-interventional registry to assess safety and effectiveness of adalimumab in patients with moderately to severely active ulcerative colitis (UC)

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<sup>44</sup> In line with the revised variations regulation for any submission before 4 August 2013

## **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. Anagrelide – XAGRID (CAP) - EMEA/H/C/000480/S/0064 (without RMP)**

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Applicant: Shire Pharmaceutical Contracts Ltd.

PRAC Rapporteur: Corinne Fechant

Scope: Annual reassessment of the marketing authorisation

#### **17.1.2. Canakinumab – ILARIS (CAP) - EMEA/H/C/0001109/S/0042 (without RMP)**

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Applicant: Novartis Europharm Ltd

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

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

#### **17.2.1. Bedaquiline – SIRTURO (CAP) - EMEA/H/C/0002614/R/0010 (without RMP)**

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Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Qun-Ying Yue

Scope: Conditional renewal of the marketing authorisation

#### **17.2.2. Bosutinib – BOSULIF (CAP) - EMEA/H/C/002373/R/0019 (without RMP)**

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Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

Scope: Conditional renewal of the marketing authorisation

#### **17.2.3. Cabozantinib – COMETRIQ (CAP) - EMEA/H/C/002640/R/0017 (without RMP)**

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Applicant: TMC Pharma Services Ltd

PRAC Rapporteur: Sabine Straus

Scope: Conditional 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 3-6 November 2015 PRAC 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
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No restrictions applicable to this meeting	Full involvement
Veerle Verlinden	Alternate	Belgium	No interests declared	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			on:	
Martin Huber	Member	Germany	No interests declared	Full involvement
Valerie Strassmann	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Alternate	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Kristín Steingrímsdóttir	Member	Iceland	No interests declared	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Carmela Macchiarulo	Member	Italy	No interests declared	Full involvement
Amelia Cupelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Amy Tanti	Member	Malta	No interests declared	Full involvement
Sabine Straus	Member	Netherlands	No interests declared	Full involvement
Menno van der Elst	Alternate	Netherlands	No interests declared	Full involvement
Ingebjørg Buajordet	Member via telephone	Norway	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
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Miroslava Matíková	Alternate	Slovakia	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Gabriela Jazbec	Alternate	Slovenia	No interests declared	Full involvement
Dolores Montero Corominas	Member	Spain	No interests declared	Full involvement
Miguel-Angel Macia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Qun-Ying Yue	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Rafe Suvarna	Alternate	United Kingdom	No interests declared	Full involvement
Jane Ahlqvist Rastad	Member	Independent scientific expert	No interests declared	Full 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
Filip Babylon	Member	Healthcare Professionals' Representative	No restrictions applicable to this meeting	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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Marco Greco	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Xavier Goossens - reporting inspector	Expert - via telephone*	Belgium	No restrictions applicable to this meeting	Full involvement
Arnaud Batz	Expert - via telephone*	France	No interests declared	Full involvement
Ridha Belaiba	Expert - via telephone*	France	No interests declared	Full involvement
Florence Cardona	Expert - via telephone*	France	No interests declared	Full involvement
Philippe Zamia	Expert - via telephone*	France	No restrictions applicable to this meeting	Full involvement
Dirk Mentzer	Expert - via telephone*	Germany	No interests declared	Full involvement
Niamh Buckley	Expert - in person*	Ireland	No interests declared	Full involvement
Zane Stade	Expert - in person*	Latvia	No interests declared	Full involvement
Maarten Lagendijk	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Miriam Verčinská	Expert - in person*	Slovakia	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Charlotta Bergquist	Expert - via telephone*	Sweden	No interests declared	Full involvement
Rolf Gedeborg	Expert - in person*	Sweden	No interests declared	Full involvement
Vidar Wendel-Hansen	Expert - in person*	Sweden	No restrictions applicable to this meeting	Full involvement
Anne Ambrose	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
Patrick Batty	Expert - via telephone*	United Kingdom	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Philip Bryan	Expert - in person*	United Kingdom	No interests declared	Full involvement
Jo Lyn Chooi	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Valerie Joynson	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Andrew Pollard - SAG chair	Expert - via telephone*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Andrew Ruddick	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Suzie Seabroke	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=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

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

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

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