



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

6 September 2018  
EMA/PRAC/576790/2018  
Inspections, Human Medicines Pharmacovigilance and Committees Division

## Pharmacovigilance Risk Assessment Committee (PRAC)

### Minutes of the meeting on 09-12 July 2018

Chair: June Raine – Vice-Chair: Almath Spooner

#### Health and safety information

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

#### Disclaimers

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

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

#### Note on access to documents

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



# Table of contents

<b>1.</b>	<b>Introduction</b>	<b>15</b>
1.1.	Welcome and declarations of interest of members, alternates and experts .....	15
1.2.	Agenda of the meeting on 09-12 July 2018 .....	15
1.3.	Minutes of the previous meeting on 11-14 June 2018 .....	15
<b>2.</b>	<b>EU referral procedures for safety reasons: urgent EU procedures</b>	<b>16</b>
2.1.	Newly triggered procedures .....	16
2.2.	Ongoing procedures .....	16
2.3.	Procedures for finalisation.....	16
<b>3.</b>	<b>EU referral procedures for safety reasons: other EU referral procedures</b>	<b>16</b>
3.1.	Newly triggered procedures .....	16
3.2.	Ongoing procedures .....	16
3.2.1.	Fluoroquinolones for systemic and inhalation use: Ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452 .....	16
3.3.	Procedures for finalisation.....	17
3.3.1.	Radium ( <sup>223</sup> Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459 .....	17
3.4.	Re-examination procedures.....	19
3.5.	Others .....	19
<b>4.</b>	<b>Signals assessment and prioritisation</b>	<b>20</b>
4.1.	New signals detected from EU spontaneous reporting systems .....	20
4.2.	New signals detected from other sources .....	20
4.2.1.	Certolizumab pegol – CIMZIA (CAP); etanercept – ENBREL (CAP), LIFMIOR (CAP); golimumab – SIMPONI (CAP); infliximab – REMICADE (CAP) .....	20
4.2.2.	Amitriptyline (NAP); dosulepin (NAP); oxybutynin - KENTERA (CAP), NAP; paroxetine (NAP); procyclidine (NAP); tolterodine (NAP) .....	21
4.2.3.	Propranolol (NAP) .....	23
4.2.4.	Sildenafil – GRANPIDAM (CAP), MYSILDECARD (CAP), REVATIO (CAP), SILDENAFIL ACTAVIS (CAP), SILDENAFIL RATIOPHARM (CAP), SILDENAFIL TEVA (CAP), VIAGRA (CAP), VIZARSIN (CAP); NAP .....	24
4.3.	Signals follow-up and prioritisation.....	26
4.3.1.	Fluoroquinolones: Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) .....	26
4.3.2.	Levothyroxine (NAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP) .....	27
4.3.3.	Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/SDA/091, NAP; abacavir, dolutegravir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/SDA/008; abacavir, lamivudine - KIVEXA	

(CAP) - EMEA/H/C/000581/SDA/047, NAP; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/SDA/092, NAP; atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/SDA/087; atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/SDA/004; bicitgravir, emtricitabine, tenofovir alafenamide – BIKTARVY (CAP); darunavir - PREZISTA (CAP) - EMEA/H/C/000707/SDA/074; darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/SDA/006; darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/SDA/012; didanosine (NAP); dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/SDA/010; dolutegravir, rilpivirine – JULUCA (CAP); efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/SDA/072.1, SUSTIVA (CAP) - EMEA/H/C/000249/SDA/083.1, NAP; efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/SDA/043.1; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide – GENVOYA (CAP); elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP); emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/SDA/052.1; emtricitabine, rilpivirine, tenofovir alafenamide – ODEFSEY (CAP); emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP); emtricitabine, tenofovir alafenamide – DESCOVY (CAP); emtricitabine, tenofovir disoproxil – TRUVADA (CAP), NAP; enfuvirtide - FUZEON (CAP) - EMEA/H/C/000514/SDA/115; etravirine - INTELENCE (CAP) - EMEA/H/C/000900/SDA/051; fosamprenavir - TELZIR (CAP) - EMEA/H/C/000534/SDA/077; indinavir - CRIXIVAN (CAP) - EMEA/H/C/000128/SDA/040; lamivudine - EPIVIR (CAP) - EMEA/H/C/000107/SDA/054, NAP; lamivudine, tenofovir (NAP); lamivudine, zidovudine - COMBIVIR (CAP) - EMEA/H/C/000190/SDA/040, NAP; lopinavir, ritonavir – KALETRA (CAP); maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/SDA/042; nevirapine - VIRAMUNE (CAP) - EMEA/H/C/000183/SDA/062; raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/SDA/058; rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/SDA/027; ritonavir – NORVIR (CAP), NAP; saquinavir - INVIRASE (CAP) - EMEA/H/C/000113/SDA/066; stavudine - ZERIT (CAP) - EMEA/H/C/000110/SDA/065; tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/SDA/275.1, NAP; tipranavir - APTIVUS (CAP) - EMEA/H/C/000631/SDA/070; zidovudine (NAP) ..... 28

4.3.4. Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestrel acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP) ..... 29

4.3.5. Human normal immunoglobulin – FLEBOGAMMA DIF (CAP), HIZENTRA (CAP), HYQVIA (CAP), KIOVIG (CAP), PRIVIGEN (CAP); NAP ..... 30

4.3.6. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP) ..... 31

## 5. Risk management plans (RMPs) 32

### 5.1. Medicines in the pre-authorisation phase ..... 32

5.1.1. Buprenorphine - EMEA/H/C/004651 ..... 32

5.1.2. Galcanezumab - EMEA/H/C/004648 ..... 33

5.1.3. Influenza vaccine surface antigen inactivated prepared in cell cultures - EMEA/H/C/004814 ..... 33

5.1.4.	Mogamulizumab - EMEA/H/C/004232, Orphan.....	33
5.1.5.	Pacritinib - EMEA/H/C/004793, Orphan .....	33
5.1.6.	Ropeginterferon alfa - EMEA/H/C/004128, Orphan.....	33
<b>5.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures.....</b>	<b>33</b>
5.2.1.	Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0055 .....	33
5.2.2.	Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0214.....	34
5.2.3.	Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0133 .....	35
<b>5.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures .....</b>	<b>36</b>
5.3.1.	Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan .....	36
<b>6.</b>	<b>Periodic safety update reports (PSURs) .....</b>	<b>37</b>
<b>6.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only .....</b>	<b>37</b>
6.1.1.	Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201712 .....	37
6.1.2.	Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201801 .....	37
6.1.3.	Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201801.....	38
6.1.4.	Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201712 .....	39
6.1.5.	Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201712 .....	40
6.1.6.	Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201712 .....	41
6.1.7.	Ustekinumab - STELARA (CAP) - PSUSA/00003085/201712 .....	41
<b>6.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>42</b>
6.2.1.	Lutetium ( <sup>177</sup> Lu) chloride - ENDOLUCINBETA (CAP), LUMARK (CAP); NAP - PSUSA/00010391/201712 .....	43
<b>6.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>43</b>
6.3.1.	Abciximab (NAP) - PSUSA/00000014/201711.....	43
6.3.2.	Furosemide, spironolactone (NAP) - PSUSA/00001493/201712 .....	44
6.3.3.	Hydroxycarbamide (NAP) - PSUSA/00009182/201712.....	45
6.3.4.	Iron (NAP) - PSUSA/00010236/201801 .....	46
6.3.5.	Lamotrigine (NAP) - PSUSA/00001825/201711 .....	47
6.3.6.	Mizolastine (NAP) - PSUSA/00002078/201711.....	47
6.3.7.	Paroxetine (NAP) - PSUSA/00002319/201712 .....	48
6.3.8.	Phenylephrine, tropicamide (NAP) - PSUSA/00010430/201711.....	49
6.3.9.	Propofol (NAP) - PSUSA/00002555/201711.....	49
6.3.10.	Rosuvastatin (NAP) - PSUSA/00002664/201711 .....	50
6.3.11.	Tapentadol (NAP) - PSUSA/00002849/201711 .....	51
<b>6.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>52</b>
<b>7.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>52</b>
<b>7.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>52</b>

7.1.1.	Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064 .....	52
<b>7.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>53</b>
<b>7.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s) .....</b>	<b>53</b>
7.3.1.	Domperidone (NAP) - EMEA/H/N/PSR/J/0010 .....	53
<b>7.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>54</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>54</b>
<b>7.6.</b>	<b>Others .....</b>	<b>54</b>
<b>7.7.</b>	<b>New Scientific Advice .....</b>	<b>54</b>
<b>7.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>55</b>
<b>7.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>55</b>
<b>8.</b>	<b>Renewals of the marketing authorisation, conditional renewal and annual reassessments .....</b>	<b>55</b>
<b>8.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>55</b>
<b>8.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>55</b>
<b>8.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>55</b>
8.3.1.	Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/R/0053 (without RMP) .....	55
<b>9.</b>	<b>Product related pharmacovigilance inspections .....</b>	<b>56</b>
<b>9.1.</b>	<b>List of planned pharmacovigilance inspections .....</b>	<b>56</b>
9.1.1.	Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products .....	56
<b>9.2.</b>	<b>Ongoing or concluded pharmacovigilance inspections .....</b>	<b>56</b>
<b>9.3.</b>	<b>Others .....</b>	<b>56</b>
<b>10.</b>	<b>Other safety issues for discussion requested by the CHMP or the EMA .....</b>	<b>56</b>
<b>10.1.</b>	<b>Safety related variations of the marketing authorisation .....</b>	<b>56</b>
10.1.1.	Raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/II/0073 .....	56
<b>10.2.</b>	<b>Timing and message content in relation to Member States' safety announcements .....</b>	<b>58</b>
<b>10.3.</b>	<b>Other requests .....</b>	<b>58</b>
<b>10.4.</b>	<b>Scientific Advice – PRAC consultation .....</b>	<b>58</b>
<b>11.</b>	<b>Other safety issues for discussion requested by the Member States .....</b>	<b>58</b>
<b>11.1.</b>	<b>Safety related variations of the marketing authorisation .....</b>	<b>58</b>
11.1.1.	Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034 .....	58
<b>11.2.</b>	<b>Other requests .....</b>	<b>59</b>
11.2.1.	Flecainide (NAP) - NO/H/PSUFU/00001396/201706 .....	59
11.2.2.	Fluoxetine (NAP) - FR/H/PSUFU/00001442/201709 .....	60

<b>12.</b>	<b>Organisational, regulatory and methodological matters</b>	<b>61</b>
<b>12.1.</b>	<b>Mandate and organisation of the PRAC</b>	<b>61</b>
12.1.1.	PRAC Chairperson - election	61
12.1.2.	PRAC working group - Best practice guide – recommendations on efficiency of plenary meetings - implementation	61
<b>12.2.</b>	<b>Coordination with EMA scientific committees or CMDh-v</b>	<b>61</b>
<b>12.3.</b>	<b>Coordination with EMA Working Parties/Working Groups/Drafting Groups</b>	<b>61</b>
<b>12.4.</b>	<b>Cooperation within the EU regulatory network</b>	<b>62</b>
12.4.1.	Reflection paper on the use of extrapolation in the development of medicines for paediatrics	62
<b>12.5.</b>	<b>Cooperation with International Regulators</b>	<b>62</b>
<b>12.6.</b>	<b>Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee</b>	<b>62</b>
<b>12.7.</b>	<b>PRAC work plan</b>	<b>62</b>
12.7.1.	PRAC work plan 2018 – status update	62
<b>12.8.</b>	<b>Planning and reporting</b>	<b>62</b>
12.8.1.	European Commission (EC) report on performance of pharmacovigilance tasks - second three-yearly report	62
12.8.2.	EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q2 2018 and predictions	63
12.8.3.	Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q2 2018	63
12.8.4.	PRAC workload statistics – Q2 2018	63
<b>12.9.</b>	<b>Pharmacovigilance audits and inspections</b>	<b>63</b>
12.9.1.	Pharmacovigilance systems and their quality systems	63
12.9.2.	Pharmacovigilance inspections	63
12.9.3.	Pharmacovigilance audits	63
<b>12.10.</b>	<b>Periodic safety update reports (PSURs) &amp; Union reference date (EURD) list</b>	<b>63</b>
12.10.1.	Periodic safety update reports single assessment (PSUSA) –Section on other considerations and follow-up procedures (PSUFU) for nationally approved products (NAPs)	63
12.10.2.	Periodic safety update reports	64
12.10.3.	Granularity and Periodicity Advisory Group (GPAG)	64
12.10.4.	PSURs repository	64
12.10.5.	Union reference date list – consultation on the draft list	64
<b>12.11.</b>	<b>Signal management</b>	<b>64</b>
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group	64
<b>12.12.</b>	<b>Adverse drug reactions reporting and additional monitoring</b>	<b>65</b>
12.12.1.	Management and reporting of adverse reactions to medicinal products	65
12.12.2.	Additional monitoring	65
12.12.3.	List of products under additional monitoring – consultation on the draft list	65

<b>12.13.</b>	<b>EudraVigilance database.....</b>	<b>65</b>
12.13.1.	Activities related to the confirmation of full functionality .....	65
12.13.2.	EudraVigilance (EV) - Clarification for MAHs on recording of individual case safety reports (ICSRs) accessed in EV .....	65
<b>12.14.</b>	<b>Risk management plans and effectiveness of risk minimisations.....</b>	<b>65</b>
12.14.1.	Risk management systems .....	65
12.14.2.	Tools, educational materials and effectiveness measurement of risk minimisations .....	65
<b>12.15.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>66</b>
12.15.1.	Post-authorisation Safety Studies – imposed PASS .....	66
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS .....	66
<b>12.16.</b>	<b>Community procedures.....</b>	<b>66</b>
12.16.1.	Referral procedures for safety reasons .....	66
<b>12.17.</b>	<b>Renewals, conditional renewals, annual reassessments .....</b>	<b>66</b>
<b>12.18.</b>	<b>Risk communication and transparency .....</b>	<b>66</b>
12.18.1.	Public participation in pharmacovigilance .....	66
12.18.2.	Safety communication .....	66
<b>12.19.</b>	<b>Continuous pharmacovigilance .....</b>	<b>66</b>
12.19.1.	Incident management .....	66
<b>12.20.</b>	<b>Others .....</b>	<b>66</b>
12.20.1.	Centrally authorised products (CAP) - implementation of electronic signature(s) for divergent position(s) in procedures adopted by majority.....	66
12.20.2.	EMA relocation to Amsterdam, the Netherlands - update .....	67
12.20.3.	Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations IV: ‘Paediatric pharmacovigilance’ .....	67
12.20.4.	Medical device and in vitro diagnostic regulation - EMA implementation plan for the new legislation.....	67
12.20.5.	Strategy on measuring the impact of pharmacovigilance - update on prioritised impact research topics.....	67
<b>13.</b>	<b>Any other business .....</b>	<b>68</b>
<b>14.</b>	<b>Annex I – Signals assessment and prioritisation .....</b>	<b>68</b>
<b>14.1.</b>	<b>New signals detected from EU spontaneous reporting systems .....</b>	<b>68</b>
14.1.1.	Dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) .....	68
14.1.2.	Montelukast (NAP) .....	68
14.1.3.	Pembrolizumab – KEYTRUDA (CAP).....	68
14.1.4.	Perindopril (NAP) .....	69
<b>14.2.</b>	<b>New signals detected from other sources .....</b>	<b>69</b>
14.2.1.	Olmesartan (NAP).....	69
14.2.2.	Ranibizumab – LUCENTIS (CAP) .....	69
14.2.3.	Thiamazole (NAP) .....	69
14.2.4.	Vemurafenib – ZELBORAF (CAP) .....	69



<b>15.</b>	<b>Annex I – Risk management plans</b>	<b>70</b>
<b>15.1.</b>	<b>Medicines in the pre-authorisation phase</b>	<b>70</b>
15.1.1.	Axalimogene filolisbac - EMEA/H/C/004473	70
15.1.2.	Doxorubicin hydrochloride - EMEA/H/C/004110	70
15.1.3.	Pegfilgrastim - EMEA/H/C/004802	70
<b>15.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures</b>	<b>70</b>
15.2.1.	Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0023	70
15.2.2.	Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/II/0086	70
15.2.3.	Bosutinib - BOSULIF (CAP) - EMEA/H/C/002373/II/0030	71
15.2.4.	Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0060	71
15.2.5.	Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0051	71
15.2.6.	Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0078	71
15.2.7.	Nilotinib - TASIGNA (CAP) - EMEA/H/C/000798/II/0092, Orphan	72
15.2.8.	Osimertinib - TAGRISSO (CAP) - EMEA/H/C/004124/II/0023	72
15.2.9.	Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/II/0099	72
15.2.10.	Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/II/0144	72
15.2.11.	Zoledronic acid - ZOLEDRONIC ACID MYLAN (CAP) - EMEA/H/C/002482/WS1370/0015	73
<b>15.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures</b>	<b>73</b>
15.3.1.	Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/X/0117/G	73
15.3.2.	Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0011, Orphan	73
15.3.3.	Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0034	73
15.3.4.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/II/0034	74
15.3.5.	Daratumumab - DARZALEX (CAP) - EMEA/H/C/004077/II/0011, Orphan	74
15.3.6.	Decitabine - DACOGEN (CAP) - EMEA/H/C/002221/II/0033, Orphan	74
15.3.7.	Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0004/G	75
15.3.8.	Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0049	75
15.3.9.	Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0005/G	75
15.3.10.	Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/II/0002	76
15.3.11.	Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0039/G	76
15.3.12.	Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS1406/0070; BINOCRIT (CAP) - EMEA/H/C/000725/WS1406/0070; EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS1406/0069	77
15.3.13.	Erlotinib - TARCEVA (CAP) - EMEA/H/C/000618/II/0058	77
15.3.14.	Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/X/0044/G	77
15.3.15.	Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0002/G	77
15.3.16.	Human coagulation factor X - COAGADEX (CAP) - EMEA/H/C/003855/II/0007, Orphan	78
15.3.17.	Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0209	78



15.3.18.	Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1278/0042; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1278/0053 .....	78
15.3.19.	Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1372/0053; Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1372/0057 .....	79
15.3.20.	Lenvatinib - KISPLYX (CAP) - EMEA/H/C/004224/WS1396/0011; LENVIMA (CAP) - EMEA/H/C/003727/WS1396/0015.....	79
15.3.21.	Mepolizumab - NUCALA (CAP) - EMEA/H/C/003860/II/0013/G .....	79
15.3.22.	Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0002 .....	79
15.3.23.	Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0047 .....	80
15.3.24.	Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS1335/0010; RIXIMYO (CAP) - EMEA/H/C/004729/WS1335/0010.....	80
15.3.25.	Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0058 .....	80
15.3.26.	Rolapitant - VARUBY (CAP) - EMEA/H/C/004196/II/0007/G .....	80
15.3.27.	Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/X/0039 .....	81
15.3.28.	Sevelamer carbonate - SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/X/0011 .....	81
15.3.29.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012 .....	81
15.3.30.	Trastuzumab - HERZUMA (CAP) - EMEA/H/C/002575/II/0006 .....	81
15.3.31.	Vismodegib - ERIVEDGE (CAP) - EMEA/H/C/002602/II/0039/G .....	82

## **16. Annex I - Periodic safety update reports (PSURs) 82**

<b>16.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only .....</b>	<b>82</b>
16.1.1.	Adalimumab - AMGEVITA (CAP), CYLTEZO (CAP), IMRALDI (CAP), SOLYMBIC (CAP) - PSUSA/00010589/201712 .....	82
16.1.2.	Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201712 .....	82
16.1.3.	Alectinib - ALECENSA (CAP) - PSUSA/00010581/201801 .....	83
16.1.4.	Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201712 .....	83
16.1.5.	Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201801 .....	83
16.1.6.	Asparaginase alfa - SPECTRILA (CAP) - PSUSA/00010455/201801 .....	83
16.1.7.	Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - PSUSA/00010617/201801 .....	83
16.1.8.	Birch bark extract - EPISALVAN (CAP) - PSUSA/00010446/201801 .....	83
16.1.9.	Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201801 .....	83
16.1.10.	Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201801 .....	84
16.1.11.	Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201712 .....	84
16.1.12.	Darunavir - PREZISTA (CAP) - PSUSA/00000934/201712 .....	84
16.1.13.	Dimethyl fumarate - SKILARENCE (CAP) - PSUSA/00010647/201712.....	84
16.1.14.	Edotreotide - SOMAKIT TOC (CAP) - PSUSA/00010552/201712.....	84
16.1.15.	Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201801 .....	84
16.1.16.	Epoetin zeta - RETACRIT (CAP), SILAPO (CAP) - PSUSA/00001241/201712 .....	84
16.1.17.	Eptacog alfa - NOVOSEVEN (CAP) - PSUSA/00001245/201712 .....	85

16.1.18.	Human fibrinogen, human thrombin - EVICEL (CAP), RAPLIXA, TACHOSIL (CAP), VERASEAL (CAP) - PSUSA/00010297/201712 .....	85
16.1.19.	Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201712 .....	85
16.1.20.	Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201712 .....	85
16.1.21.	Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201712.....	85
16.1.22.	Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201712 .....	85
16.1.23.	Liraglutide - SAXENDA (CAP), VICTOZA (CAP) - PSUSA/00001892/201712.....	85
16.1.24.	Lutetium ( <sup>177</sup> Lu) oxodotreotide - LUTATHERA (CAP) - PSUSA/00010643/201712 .....	86
16.1.25.	Matrix-applied characterised autologous cultured chondrocytes - MACI - PSUSA/00010116/201712 .....	86
16.1.26.	Nonacog gamma - RIXUBIS (CAP) - PSUSA/00010320/201712 .....	86
16.1.27.	Obeticholic acid - OCALIVA (CAP) - PSUSA/00010555/201712 .....	86
16.1.28.	Olaparib - LYNPARZA (CAP) - PSUSA/00010322/201712.....	86
16.1.29.	Opicapone - ONGENTYS (CAP) - PSUSA/00010516/201712.....	86
16.1.30.	Pegaspargase - ONCASPAR (CAP) - PSUSA/00010457/201801 .....	87
16.1.31.	Reteplase - RAPILYSIN (CAP) - PSUSA/00002623/201711 .....	87
16.1.32.	Roflumilast - DAXAS (CAP) - PSUSA/00002658/201801.....	87
16.1.33.	Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201712.....	87
16.1.34.	Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201801 .....	87
16.1.35.	Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201712 .....	87
16.1.36.	Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201712 .....	87
16.1.37.	Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201801.....	88
16.1.38.	Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201712 .....	88
16.1.39.	Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201801 .....	88
16.1.40.	Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201801.....	88
16.1.41.	Umeclidinium bromide, vilanterol - ANORO (CAP), LAVENTAIR (CAP) - PSUSA/00010264/201712 .....	88
16.1.42.	Riluzole - RILUTEK (CAP), RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/201712....	88
<b>16.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs) .....</b>	<b>89</b>
16.2.1.	Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201711 .	89
<b>16.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>89</b>
16.3.1.	Alfuzosin (NAP) - PSUSA/00000084/201711 .....	89
16.3.2.	Amino acid combinations, glucose, triglyceride combinations, with or without electrolytes, mineral compounds (NAP) - PSUSA/00010190/201712.....	89
16.3.3.	Amlodipine, indapamide (NAP); amlodipine, indapamide, perindopril (NAP) - PSUSA/00010358/201711 .....	89
16.3.4.	Antithrombin III (NAP) - PSUSA/00003159/201712 .....	89

16.3.5.	Bambuterol (NAP) - PSUSA/00000295/201712 .....	89
16.3.6.	Bromperidol (NAP) - PSUSA/00000439/201711 .....	90
16.3.7.	Caffeine, drotaverine hydrochloride, metamizol sodium (NAP) - PSUSA/00001996/201711 .....	90
16.3.8.	Cetirizine (NAP) - PSUSA/00000628/201711 .....	90
16.3.9.	Ciprofloxacin hydrochloride, hydrocortisone (NAP) - PSUSA/00000774/201711 .....	90
16.3.10.	Clevidipine (NAP) - PSUSA/00010288/201711 .....	90
16.3.11.	Diacerein (NAP) - PSUSA/00001026/201712 .....	90
16.3.12.	Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001124/201711 .....	90
16.3.13.	Dutasteride (NAP); dutasteride, tamsulosine (NAP) - PSUSA/00010506/201711 .....	91
16.3.14.	Econazole (NAP); econazole nitrate, triamcinolone acetonide (NAP); econazole nitrate, zinc oxide (NAP) - PSUSA/00001195/201711 .....	91
16.3.15.	Fludeoxyglucose ( <sup>18</sup> F) (NAP) - PSUSA/00001437/201711 .....	91
16.3.16.	Glatiramer (NAP) - PSUSA/00001529/201711 .....	91
16.3.17.	Levocabastine (NAP) - PSUSA/00001849/201711 .....	91
16.3.18.	Methylprednisolone (NAP) - PSUSA/00002026/201711 .....	91
16.3.19.	Rupatadine (NAP) - PSUSA/00002673/201712 .....	91
16.3.20.	Tafluprost, timolol (NAP) - PSUSA/00010324/201712 .....	92
<b>16.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>92</b>
16.4.1.	Oxybutynin - KENTERA (CAP) - EMEA/H/C/000532/LEG 022 .....	92
16.4.2.	Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037.2 .....	92
<b>17.</b>	<b>Annex I – Post-authorisation safety studies (PASS) .....</b>	<b>92</b>
<b>17.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s) .....</b>	<b>92</b>
17.1.1.	Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSP/S/0057.1 .....	92
17.1.2.	Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/PSP/S/0065 .....	93
17.1.3.	Valproate (NAP) - EMEA/H/N/PSA/J/0015.3 .....	93
<b>17.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>93</b>
17.2.1.	Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.4 .....	93
17.2.2.	Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012.3 .....	93
17.2.3.	Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013.2 .....	94
17.2.4.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.4 .....	94
17.2.5.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.3 .....	94
17.2.6.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 012.2 .....	94
17.2.7.	Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.1 .....	95
17.2.8.	Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/MEA 003.2 .....	95
17.2.9.	Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019.2 .....	95
17.2.10.	Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007.2 .....	95
17.2.11.	Denosumab - XGEVA (CAP) - EMEA/H/C/002173/MEA 026 .....	96

17.2.12.	Elbasvir, grazoprevir - ZEPATIER (CAP) - EMEA/H/C/004126/MEA 004.2 .....	96
17.2.13.	Emicizumab - HEMLIBRA (CAP) - EMEA/H/C/004406/MEA 001 .....	96
17.2.14.	Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMEA/H/C/000594/MEA 045.5 .....	96
17.2.15.	Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.1 .....	97
17.2.16.	Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002.....	97
17.2.17.	Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005.....	97
17.2.18.	Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 006.....	97
17.2.19.	Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/MEA 017.2 .....	98
17.2.20.	Meningococcal group B vaccine (recombinant, adsorbed) - TRUMENBA (CAP) - EMEA/H/C/004051/MEA 003 .....	98
17.2.21.	Naloxegol - MOVENTIG (CAP) - EMEA/H/C/002810/MEA 006.5 .....	98
17.2.22.	Niraparib - ZEJULA (CAP) - EMEA/H/C/004249/MEA 003.....	98
17.2.23.	Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.2 .....	99
17.2.24.	Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059 .....	99
17.2.25.	Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 004.2 .....	99
17.2.26.	Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.7 .....	99
17.2.27.	Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.2.....	100
17.2.28.	Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.2 .....	100
17.2.29.	Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/MEA 002.1 .....	100
<b>17.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s) .....</b>	<b>100</b>
<b>17.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>101</b>
17.4.1.	Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0062/G, Orphan.....	101
17.4.2.	Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0070/G .....	101
<b>17.5.</b>	<b>Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....</b>	<b>101</b>
17.5.1.	Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.5.....	101
17.5.2.	Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.5.....	101
17.5.3.	Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/ANX 003.2 .....	102
17.5.4.	Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/ANX 003.2 .....	102
17.5.5.	Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/MEA 002.3 .....	102
17.5.6.	Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/MEA 010.3 .....	102
17.5.7.	Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.3 .....	103
17.5.8.	Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 001.3.....	103
17.5.9.	Florbetapir ( <sup>18</sup> F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.5 .....	103
17.5.10.	Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.6 .....	103
17.5.11.	Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.7.....	104
17.5.12.	Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001.3 .....	104

17.5.13.	Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.3 .....	104
17.5.14.	Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.3 .....	104
17.5.15.	Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002.....	105
17.5.16.	Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.....	105
17.5.17.	Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.11 .....	105
<b>17.6.</b>	<b>Others .....</b>	<b>105</b>
17.6.1.	Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.9 .....	105
17.6.2.	Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.9 .....	106
17.6.3.	Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 001.4 .....	106
17.6.4.	Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/MEA 065.3 .....	106
17.6.5.	Desloratadine - AZOMYR (CAP) - EMEA/H/C/000310/MEA 065.3 .....	106
17.6.6.	Desloratadine - NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA 065.3 .....	107
17.6.7.	Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 005 .....	107
17.6.8.	Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001.4 ....	107
<b>17.7.</b>	<b>New Scientific Advice .....</b>	<b>107</b>
<b>17.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>107</b>
<b>17.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>107</b>
<b>18.</b>	<b>Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments .....</b>	<b>108</b>
<b>18.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>108</b>
18.1.1.	Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0053 (without RMP) .....	108
18.1.2.	Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0006 (without RMP) .....	108
18.1.3.	Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0006 (without RMP) .....	108
18.1.4.	Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0075 (without RMP) .....	108
<b>18.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>108</b>
18.2.1.	Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0058 (without RMP) .....	108
18.2.2.	Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0012 (without RMP) .....	109
18.2.3.	Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/R/0010 (without RMP) .....	109
18.2.4.	Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0013 (without RMP) .....	109
<b>18.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>109</b>
18.3.1.	Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/R/0044 (without RMP) ....	109
18.3.2.	Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/R/0040 (with RMP) .....	109
18.3.3.	Filgrastim - GRAFTOFIL (CAP) - EMEA/H/C/002150/R/0020 (without RMP) .....	109
18.3.4.	Florbetaben ( <sup>18</sup> F) - NEURACEQ (CAP) - EMEA/H/C/002553/R/0025 (with RMP) .....	109
18.3.5.	Levetiracetam - LEVETIRACETAM HOSPIRA (CAP) - EMEA/H/C/002783/R/0018 (without RMP) .....	110
18.3.6.	Lidocaine, prilocaine - FORTACIN (CAP) - EMEA/H/C/002693/R/0023 (with RMP) .....	110
18.3.7.	Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/R/0050 (with RMP) .....	110

18.3.8.	Stiripentol - DIACOMIT (CAP) - EMEA/H/C/000664/R/0021 (without RMP) .....	110
18.3.9.	Trastuzumab emtansine - KADCYLA (CAP) - EMEA/H/C/002389/R/0039 (without RMP) ...	110
18.3.10.	Travoprost - IZBA (CAP) - EMEA/H/C/002738/R/0011 (without RMP) .....	110
18.3.11.	Vortioxetine - BRINTELLIX (CAP) - EMEA/H/C/002717/R/0019 (with RMP) .....	110
<b>19.</b>	<b>Annex II – List of participants</b>	<b>111</b>
<b>20.</b>	<b>Annex III - List of acronyms and abbreviations</b>	<b>121</b>
<b>21.</b>	<b>Explanatory notes</b>	<b>121</b>

## **1. Introduction**

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

The Chairperson opened the 09-12 July 2018 meeting by welcoming all participants.

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

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

The PRAC Chairperson welcomed Birgitta Grundmark, Daniel Morales, Livia Puljak, Antoine Pariente and Stefan Weiler as the new independent scientific experts nominated by the European Commission, with a mandate started as of 2 July 2018. The PRAC Chairperson also noted that Hedvig Marie Egeland Nordeng was the sixth independent scientific expert who announced she will attend the PRAC from September/October 2018. In addition, the Chair welcomed Brigitte Keller-Stanislawski as the new alternate for Germany, replacing Valerie Strassmann. It was also noted that Annika Folin was the new alternate for Sweden, replacing Qun-Ying Yue. Moreover, the Chair announced that the following members were attending their last PRAC meeting: Almath Spooner as the member for Ireland and vice-Chair of the Committee, Dolores Montero Corominas as the member for Spain, Milena Radoha-Bergoc as the member for Slovenia, and Caroline Laborde as the alternate for France. Furthermore, it was noted that it was also the last meeting for June Raine, as a Chairperson of the PRAC. The Committee thanked them for their huge contribution to the work of the Committee and the European pharmacovigilance network.

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

### **1.2. Agenda of the meeting on 09-12 July 2018**

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

### **1.3. Minutes of the previous meeting on 11-14 June 2018**

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

Post-meeting note: the PRAC minutes of the meeting held on 11-14 June 2018 were published on the EMA website on 10 August 2018 ([EMA/PRAC/400242/2018](#)).



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

### 2.1. Newly triggered procedures

None

### 2.2. Ongoing procedures

None

### 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

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

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

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

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

#### Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for quinolone- and fluoroquinolone-containing medicines for systemic and inhalational use, indicated for the treatment of bacterial infections, in particular those which are serious and life-threatening, in order to assess the persistence of side effects known to occur with quinolone and fluoroquinolone antibiotics, following reports of long-lasting side effects mainly affecting musculoskeletal and nervous systems. The review also assesses the need for adequate and consistent risk minimisation measures (RMMs) as well as the impact of this safety concern if confirmed on the overall benefit-risk balance of quinolones and fluoroquinolones for systemic and inhalational use, especially in authorised indications which are related to treatment of non-serious/non-severe infections. For further background, see [PRAC minutes February 2017](#), [PRAC minutes June 2017](#), [PRAC minutes October 2017](#), [PRAC minutes November](#)

[2017](#), [PRAC minutes February 2018](#), [PRAC minutes March 2018](#), [PRAC minutes May 2018](#) and [PRAC minutes June 2018](#).

### Summary of recommendation(s)/conclusions

- The PRAC discussed the joint assessment report prepared by the Rapporteurs.
- The PRAC adopted a list of questions (LoQ) to relevant healthcare professionals and a LoQ targeted to patients. In addition, the PRAC adopted a third list of outstanding issues (LoOI) to be addressed by the MAHs for quinolone- and fluoroquinolone- containing medicinal products together with a revised timetable for conducting the review ([EMA/PRAC/38618/2017 Rev. 6](#)).
- The PRAC welcomed the presentation by EMA on the outcome of the survey of attendees at the public hearing held on 13 June 2018.

## 3.3. Procedures for finalisation

### 3.3.1. Radium (<sup>223</sup>Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459

---

Applicant: Bayer AG

PRAC Rapporteur: Patrick Batty; PRAC Co-rapporteur: Martin Huber

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

#### Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for Xofigo (radium-223 dichloride), to review the results of a phase 3 study (ERA 223<sup>1</sup>) and assess their potential impact on the benefit-risk balance of Xofigo (radium-223 dichloride) in the authorised indication of the treatment of castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases, is to be concluded. The review was started after analyses of uncleaned preliminary data from this clinical trial, evaluating Xofigo (radium-223 dichloride) in combination with abiraterone acetate and prednisone/prednisolone in chemotherapy-naïve patients with asymptomatic or mildly symptomatic bone predominant metastatic castrate-resistant prostate cancer, found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). For further background, see [PRAC minutes December 2017](#), [PRAC minutes March 2018](#), [PRAC minutes May 2018](#) and [PRAC minutes June 2018](#). A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

#### Discussion

The PRAC discussed the conclusions reached by the Rapporteurs.

---

<sup>1</sup> Study 15396 (ERA-223) (NCT02043678): a phase 3, randomised, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

The PRAC reviewed the preliminary data analyses of study ERA-223 that showed an increased risk of fracture and a trend for an increased risk of mortality compared to placebo when radium-223 treatment was combined with abiraterone acetate and prednisone/prednisolone treatment. The PRAC also considered all other available data, including data from the ALSYMPCA<sup>2</sup> clinical trial which supported the initial marketing authorisation and the data provided by the MAH at an oral explanation, in relation to the potential impact of the results of study ERA-223 on the benefit-risk balance of Xofigo (radium-223) in the authorised indication. The PRAC also considered the views expressed by the Scientific Advisory Group on oncology ([SAG-O](#)).

The PRAC noted that the use of radium-223 in ERA-223 took place in chemotherapy-naïve patients at earlier stages of the disease, albeit partially overlapping with that included in the authorised indication. Considering all available data, the PRAC concluded that radium-223 is associated with an increased risk of fracture during treatment and for several months after the end of treatment. The PRAC also considered that the results of ERA-223 added to the uncertainties regarding the extent of benefit noted in ALSYMPCA at the time of initial marketing authorisation, in particular in patients with a lower disease burden and in light of the uncertainties regarding the potential for radium-223 to promote non-bone disease progression. Therefore, the PRAC considered that measures are needed to minimise these risks associated with Xofigo (radium-223 dichloride) treatment including preventing the use of the product in similar settings to that of ERA-223. As a consequence, the PRAC recommended that the indication of Xofigo (radium-223 dichloride) is restricted to use as monotherapy or in combination with a luteinising hormone releasing hormone (LHRH) analogue, for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment. The PRAC further confirmed that Xofigo (radium-223 dichloride) should remain contraindicated in combination with abiraterone acetate and prednisone/prednisolone as recommended in the provisional measures adopted in March 2018.

In addition, considering the increased risk of fracture and a possible increase in mortality, the PRAC recommended not to use Xofigo (radium-223 dichloride) in patients with only asymptomatic bone metastases or in combination with other systemic active cancer therapies. Treatment-free intervals before and after treatment with Xofigo (radium-223 dichloride) are recommended. In view of the increased risk of fracture, the uncertainties raised, and the absence of significant evidence that the benefits observed in ALSYMPCA apply to patients with a low level of osteoblastic bone metastases, the PRAC recommended not to use Xofigo (radium-223 dichloride) in these patients, and in patients with mildly symptomatic bone metastases, to use Xofigo (radium-223 dichloride) only if the benefits are expected to outweigh the risks.

Furthermore, the PRAC considered that in order to minimise the risk of fracture, healthcare professionals should assess bone status and baseline risk of fracture for all patients prior to initiating Xofigo (radium-223 dichloride) and monitor patients for at least 24 months. The use of bisphosphonates or denosumab should be considered. In patients at high risk of

---

<sup>2</sup> ALSYMPCA clinical trial: a double-blind, randomised, multiple dose, phase 3, multicentre study of alpharadin in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases. NCT00699751. EudraCT number: 2007-006195-11

fracture, Xofigo (radium-223 dichloride) should only be initiated if the expected benefits are considered to outweigh the risks associated with treatment.

Finally, the PRAC recommended imposing as conditions to the marketing authorisation of Xofigo (radium-223 dichloride) the conduct of a randomised controlled clinical trial, a non-interventional PASS and a biodistribution study, in order to further characterise the safety and efficacy of Xofigo (radium-223 dichloride), including the mechanisms responsible for the increased risk of fracture, and the possible risk of increased mortality reported in ERA-223.

In view of the above, the Committee considered that the benefit-risk balance of Xofigo (radium-223 dichloride) remains favourable subject to the agreed conditions to the marketing authorisation, and taking into account the agreed amendments to the product information.

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

- The PRAC adopted, by majority<sup>3</sup>, a recommendation to vary<sup>4</sup> the terms of the marketing authorisations for Xofigo (radium-223 dichloride) to be considered by CHMP for an opinion – see EMA Press Release ([EMA/472321/2018](#)) entitled ‘PRAC recommends restricting use of prostate cancer medicine Xofigo - Medicine should only be used after two previous treatments or when other treatments cannot be taken’.
- The PRAC agreed the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Twenty-four members voted in favour of the recommendation whilst seven members<sup>5</sup> had divergent views<sup>6</sup>. The Icelandic PRAC member agreed with the recommendation whilst the Norwegian PRAC member had a divergent view<sup>7</sup>.

Post-meeting note: the press release entitled ‘EMA restricts use of prostate cancer medicine Xofigo - Medicine to be used only after two previous treatments or when other treatments cannot be taken’ ([EMA/500948/2018](#)) representing the opinion adopted by the CHMP was published on the EMA website on 27/07/2018.

## **3.4. Re-examination procedures<sup>8</sup>**

None

## **3.5. Others**

None

---

<sup>3</sup> The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

<sup>4</sup> Update of SmPC sections 4.1, 4.3, 4.4, 4.8, and 5.1 The package leaflet is updated accordingly

<sup>5</sup> Ghania Chamouni, Amelia Cupelli, Dolores Montero Corominas, Adam Przybylkowski, Almath Spooner, Sabine Straus, Julie Williams

<sup>6</sup> The relevant AR containing the divergent views will be published on the EMA website once the procedure is fully concluded

<sup>7</sup> Karen Pernille Harg

<sup>8</sup> Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

## 4. Signals assessment and prioritisation<sup>9</sup>

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

See Annex I 14.1.

### 4.2. New signals detected from other sources

See also Annex I 14.2.

#### 4.2.1. Certolizumab pegol – CIMZIA (CAP); etanercept – ENBREL (CAP), LIFMIOR (CAP); golimumab – SIMPONI (CAP); infliximab – REMICADE (CAP)

Applicant(s): Janssen Biologics B.V. (Remicade, Simponi), Pfizer Limited (Enbrel, Lifmior), UCB Pharma S.A. (Cimzia)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of risk for lichenoid skin reactions for tumour necrosis factor alfa (TNFα) inhibitors

EPITT 19128 – New signal

Lead Member State(s): SE, UK

#### Background

Cimzia, Enbrel, Simponi and Remicade, centrally authorised medicines containing certolizumab pegol, etanercept, golimumab, and infliximab respectively, are tumour necrosis factor alfa (TNFα) inhibitors. TNFα inhibitors have various indications including the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, psoriasis, and for some treatment of Crohn's disease and ulcerative colitis; all under certain conditions.

The exposure for Cimzia (certolizumab pegol), is estimated to approximately 420,451 patient-years cumulatively, in the period from first authorisation in 2007 to 2017. The exposure for Enbrel (etanercept) is estimated to approximately 6,169,909 patient-years cumulatively, in the period from first authorisation in 1998 to 2018. The exposure for Simponi (golimumab) is estimated to approximately 600,000 patients cumulatively, in the period from first authorisation in 2009 to 2017. The exposure for Remicade (infliximab) is estimated to approximately 5,159,790 patient-years cumulatively, in the period from first authorisation in 1998 to 2016.

Following the publication in the European Journal of Dermatology of an article by *Inoue A et al.*<sup>10</sup>, a signal of lichenoid skin reactions was identified by EMA for adalimumab and a recommendation was adopted by PRAC in January 2018 (see [PRAC minutes January 2018; EPITT 19128](#)). An update of the product information (PI) in order to add lichenoid skin reactions as an undesirable effect with frequency 'rare' through a type II variation (II/0179) was concluded at CHMP in July 2018 for Humira (adalimumab). For other TNFα inhibitors,

<sup>9</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

<sup>10</sup> Inoue A, et al. Lichenoid drug eruption caused by adalimumab: a case report and literature review. Eur J Dermatol. 2017 Feb 1;27(1):69-70

cases have been reported. Following the review of the literature for all TNF $\alpha$  inhibitors, in particular the publication of *McCarty et al.*<sup>11</sup> in the Journal of Clinical and Aesthetic Dermatology (JCAD), Sweden identified a signal of risk for lichenoid skin reactions for all TNF $\alpha$  inhibitors. Sweden confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## Discussion

Having considered the available evidence for adalimumab including several case reports confirmed by biopsy results with positive dechallenge/rechallenge (see [PRAC minutes January 2018](#)), the PRAC agreed to extend the safety review to the whole class of TNF $\alpha$  inhibitors.

The MAHs for Cimzia (certolizumab pegol), Enbrel/Lifmior (etanercept), Simponi (golimumab) and Remicade (infliximab) should provide cumulative reviews of cases of lichenoid skin eruptions, including lichen planopilaris in association with their respective TNF $\alpha$  inhibitors. The MAHs should also discuss the need for any potential amendment to the product information and/or RMP.

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

## Summary of recommendation(s)

- The MAHs for Cimzia (certolizumab pegol), UCB Pharma SA, Enbrel/Lifmior (etanercept), Pfizer Limited, Simponi (golimumab) and Remicade (infliximab), Janssen Biologics B.V., should submit to EMA, within 60 days, cumulative reviews of cases of lichenoid skin eruptions, including lichen planopilaris in association with their respective TNF $\alpha$  inhibitor and including the results of histological investigations, dechallenge/rechallenge information as well as clinical data from all sources (clinical trials, spontaneous reports and relevant literature) to evaluate the biological plausibility for a possible association. The MAHs should also discuss the need for any potential amendment to the product information and/or RMP and make accordingly a proposal for changes to the relevant sections as part of the discussion.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

### 4.2.2. [Amitriptyline \(NAP\); dosulepin \(NAP\); oxybutynin - KENTERA \(CAP\), NAP; paroxetine \(NAP\); procyclidine \(NAP\); tolterodine \(NAP\)](#)

---

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

PRAC Rapporteur: Laurence de Fays

Scope: Signal of dementia

EPITT 19263 – New signal

Lead Member State(s): AT, BE, DE, ES, GR, NL, SE

## Background

---

<sup>11</sup> McCarty M et al, Lichenoid reactions in association with tumor necrosis factor alpha inhibitors, J Clin Aesthet Dermatol. 2015 Jun; 8(6):45-9

Amitriptyline is a tricyclic antidepressant (non-selective monoamine reuptake inhibitor) indicated for the treatment of major depressive disorder in adults, neuropathic pain in adults, nocturnal enuresis in children aged 6 years and above under certain conditions as well as the prophylactic treatment of chronic tension type headache (CTTH) and migraine in adults.

Dosulepin is a tricyclic antidepressant (non-selective monoamine reuptake inhibitor) indicated for the treatment of symptoms of depressive illness especially where an anti-anxiety effect is required with certain restrictions.

Kentera is a centrally authorised product containing oxybutynin, a urinary antispasmodic. Kentera (oxybutynin) is indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with unstable bladder. The cumulative exposure to oxybutynin is estimated to have been more than 52,165,608 patient-months worldwide, in the period from first authorisation in 1988 to 2017.

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) indicated for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder, social anxiety disorder (SAD)/social phobia, generalised anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and premenstrual dysphoric disorder (PMDD). The cumulative exposure to paroxetine is estimated to have been more than over 400 million patient treatments worldwide, in the period from first authorisation in 1990 to 2017.

Procyclidine is an anticholinergic indicated in all forms of Parkinson's disease: idiopathic (paralysis agitans), post encephalitic and arteriosclerotic.

Tolterodine is an antiseptic and anti-infective preparation for systemic use specifically used in urinary tract infections as well as a gastrointestinal antispasmodic, indicated for the treatment of overactive bladder (OAB) with symptoms of urinary frequency, urgency, and urge incontinence. Tolterodine is estimated to have been used by more than 19,336,731 patients worldwide cumulatively, in the period from 1997 to 2016.

Following the publication in the British Medical Journal (BMJ) of an article by *Richardson et al.*<sup>12</sup>, a signal of dementia was identified by EMA, suggesting that the risk of dementia increased with greater exposure for antidepressant, urological, and antiparkinsonian drugs. Belgium confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## Discussion

Having considered the results from the study by *Richardson et al.* and available evidence from EudraVigilance, the PRAC agreed that the current evidence does not warrant any regulatory action at this stage.

## Summary of recommendation(s)

- The PRAC agreed that the current available evidence does not warrant any regulatory action at this stage.
- The MAHs of oxybutynin-, tolterodine-, amitriptyline-, paroxetine-, dosulepin- and procyclidine-containing products should closely monitor dementia and review any data in the next PSURs.

---

<sup>12</sup> Richardson Kathryn, Fox Chris, Maidment Ian, Steel Nicholas, Loke Yoon K, Arthur Antony et al. Anticholinergic drugs and risk of dementia: case-control study BMJ 2018; 361:k1315. doi: 10.1136/bmj.k1315



Applicant(s): various

PRAC Rapporteur: Karen Pernille Harg

Scope: Signal of increased risk of Parkinson's disease

EPITT 19223 – New signal

Lead Member State(s): ES

#### Background

Propranolol is a non-selective beta blocking agent indicated<sup>13</sup> in angina pectoris, hypertension, long-term prophylaxis against myocardial reinfarction after recovery from acute myocardial infarction, hypertrophic obstructive cardiomyopathy, essential tremor, supraventricular cardiac arrhythmia, ventricular cardiac arrhythmias, hyperthyroidism and thyrotoxicosis, phaeochromocytoma (with an alpha-blocker), migraine, and prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices.

Following the publication in Science by *Mittal S et al.*<sup>14</sup>, a signal of increased risk of Parkinson's disease (PD) was identified by Norway, suggesting an increased risk of development of PD in patients who have ever used propranolol. Spain confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

Having considered the publication by *Mittal et al.* including a study in the Norwegian Prescription Database (NorPD), the PRAC agreed that the MAH of the originator propranolol-containing product should provide a cumulative review of all data relevant to the possible association between propranolol and an increased risk of PD. In addition, the PRAC agreed that the Norwegian National Competent Agency (NoMA) will provide an overview of the Norwegian prescription patterns of beta-blockers including the beta-blocker of choice in Norway and a distribution of hypertensive patients on propranolol versus other beta-adrenoceptor blocking agents. The PRAC also agreed on a list of questions to the study authors for clarification of the study findings in order to better perform an in-depth analysis of the results and assess the need for further actions on this issue.

The PRAC appointed Karen Pernille Harg as Rapporteur for the signal.

#### Summary of recommendation(s)

- The MAH for the originator propranolol-containing product, AstraZeneca AB, should submit to EMA, within 60 days, a cumulative review of all data relevant to the possible association between propranolol and an increased risk of Parkinson's disease including the published literature, mechanistic, epidemiological studies, and all clinical trials, as well as any relevant preclinical data.
- In addition, the PRAC agreed that the Norwegian NCA will provide an overview of the Norwegian prescription patterns of beta-blockers including the beta-blocker of choice in Norway and the distribution of hypertensive patients on propranolol versus other beta-adrenoceptor blocking agents.

---

<sup>13</sup> Hemangioli (propranolol), centrally authorised product, is not part of the review

<sup>14</sup> Mittal S, Bjørnevik K, Doo Soon I, et al.  $\beta$ 2-adrenoceptor is a regulator of the  $\alpha$ -synuclein gene driving risk of Parkinson's disease. Science 2017;357:891-98

- Finally, the PRAC agreed to request the authors to provide additional clarifications on their study findings in order to better perform an in depth analysis of the results and assess the need for further actions on this issue.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.2.4. Sildenafil – GRANPIDAM (CAP), MYSILDECARD (CAP), REVATIO (CAP), SILDENAFIL ACTAVIS (CAP), SILDENAFIL RATIOPHARM (CAP), SILDENAFIL TEVA (CAP), VIAGRA (CAP), VIZARSIN (CAP); NAP

---

Applicant(s): Accord Healthcare (Granpidam), Actavis Group PTC (Sildenafil Actavis), Krka, d.d., Novo mesto (Vizarsin), Mylan S.A.S (Mysildecard), Pfizer Limited (Revatio, Viagra), Ratiopharm GmbH (Sildenafil Ratiopharm), Teva B.V. (Sildenafil Teva); various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction

**Action:** For adoption of PRAC recommendation

EPITT 19287 – New signal

##### **Background**

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). Sildenafil is indicated as Viagra and its generics in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. It is also indicated as Revatio and its generics for the treatment of adult patients with pulmonary arterial hypertension classified as WHO<sup>15</sup> functional class II and III, to improve exercise capacity as well as for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

Following the notification of the Dutch clinical trials competent authority, the Central Committee on Research involving subjects ([CCMO](#)), and of the Dutch National competent Authority ([CBG-MEB](#)) of the premature termination of the Dutch-STRIDER<sup>16</sup> clinical study for safety reasons, the Netherlands circulated a non-urgent information (NUI) on 25 July 2017 that was discussed at the organisational matters teleconference held on 26 July 2018 (see 13. AOB). Taking into consideration the need for further assessment, a signal of pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction was identified by EMA. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

An international collaboration (STRIDER) was established with the aim to evaluate the effectiveness and safety of sildenafil for foetal growth restriction in a prospective individual patient data meta-analysis from a series of national randomised clinical trials using similar (but not identical) protocols and a common dataset. A total of five STRIDER trials were planned in several countries: the Netherlands, United Kingdom, Ireland, Canada and Australia/New Zealand. Although the individual trials have different primary outcomes, all trials were designed to collect a standard set of outcomes including survival without severe

---

<sup>15</sup> World Health Organization

<sup>16</sup> The Dutch STRIDER: sildenafil therapy in dismal prognosis early-onset foetal growth restriction. NCT02277132. EudraCT number: 2012-004112-63

neonatal morbidity at the time of hospital discharge. All five individual trials were to contribute to a pre-planned systematic review of the topic including individual patient data meta-analysis. The Dutch STRIDER trial aiming to evaluate the effectiveness of sildenafil (versus placebo) in achieving healthy perinatal survival, in women with singleton pregnancies with severe foetal growth restriction of placental origin, was conducted in the Netherlands since 2014 by a non-commercial sponsor (Academic Medical Centre). The data safety monitoring board (DSMB) recommended stopping its recruitment after the assessment of interim analysis data from 183 patients, of whom for 182 (93 on sildenafil and 89 on placebo) the results regarding the primary endpoint were available. The main consideration to recommend stopping is that there is a serious concern that sildenafil may cause harm to the newborn children, while at the same time the interim results of the 182 children show that it is extremely unlikely that after complete follow up any benefit can still be shown on the primary endpoint of intact neonatal survival until term age.

## Discussion

Having reviewed the available evidence from preliminary data from the STRIDER trials, including the Dutch-STRIDER trial, the PRAC agreed on 1 August 2018 by written procedure that Pfizer, the brandleader for sildenafil-containing products (Revatio, Viagra), should provide supplementary information in response to the adopted list of questions, including careful consideration of the need for communication to HCPs.

The PRAC appointed Menno van der Elst as Rapporteur for the signal.

## Summary of recommendation(s)

- The MAH should provide an overview of the extent of off-label use in the EU/EEA in pregnancy including in the indication of intrauterine growth restriction including any relevant literature, drug utilisation data, and post-marketing data, as well as addressing possible differences between EU Member States. Considering the potential off-label use and the possible risk of adverse effects, the MAH should also discuss the need to communicate to HCP and present a communication plan if warranted.
- The MAH should provide to EMA, within 10 days, a cumulative overview of the effects of sildenafil use in the off-label indication of intrauterine growth restriction, including literature, preclinical data as well as data from all finalised and on-going clinical trials (as far as data are available) together with a discussion on the need to update the product information with information on the effects of sildenafil when used by women with pregnancies complicated by severe early-onset intrauterine growth restriction.
- The MAH should make a proposal accordingly for changes to the relevant sections of the product information and the RMP within this discussion.
- In the next PSUR for Revatio (sildenafil) with a data lock point (DLP) set on 31/05/2018 due for submission no later than 29/08/2018, the MAH is requested to present a cumulative review of the use of sildenafil during pregnancy including literature, preclinical data, and clinical data as well as post marketing data and a discussion on whether any changes to the relevant sections of the product information are needed.
- A 30-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. Fluoroquinolones:

Ciprofloxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)

---

Applicant(s): Raptor Pharmaceuticals Europe BV (Quinsair), various

PRAC Rapporteur: Martin Huber

Scope: Signal of aortic aneurysm and dissection

EPITT 18651 – Related to October 2016

Lead Member State: DE

#### Background

For background information, see [PRAC minutes May 2016](#) and [PRAC minutes October 2016](#).

At its October 2016 PRAC meeting (26-29 September 2016), the PRAC, having considered the studies published by *Daneman et al.*<sup>17</sup> and *Lee et al.*<sup>18</sup> and the responses from the MAHs of systemic fluoroquinolone-containing products, agreed that there was insufficient evidence to establish an association between systemic fluoroquinolones and an increased risk of aortic aneurysm or dissection that would warrant an update of the product information. The MAHs of systemic fluoroquinolones had to continue to monitor aortic aneurysm or dissection as part of routine safety surveillance.

Following the publication in BMJ by *Pasternak et al.*<sup>19</sup>, as well as considering preliminary data from the nationwide French Health Insurance database, France reopened the signal procedure for the signal of aortic aneurysm and dissection with fluoroquinolones. Germany (BfArM) confirmed that the signal needed initial analysis and prioritisation by the PRAC.

#### Discussion

Having considered the epidemiological studies published to date (*Lee et al.* 2015, *Daneman et al.* 2015, *Pasternak et al.* 2018) as well as available non-clinical data (*LeMaire et al.* 2017), the PRAC agreed that there is sufficient evidence to reflect the risk of aortic aneurysm and dissection in the product information (PI) of systemic fluoroquinolones. The MAHs for originator systemic fluoroquinolone-containing products should comment on a proposal to update the PI to include a warning on the increased risk of aortic aneurysm and dissection observed after intake of fluoroquinolones in epidemiological studies. In addition, the MAHs should discuss the need for further risk minimisation measures and communication and make proposals accordingly. Moreover, the PRAC agreed on a list of questions (LoQ) to the study authors to receive additional information and clarifications on the study findings.

#### Summary of recommendation(s)

- The MAHs for originator systemic fluoroquinolone-containing products, i.e. Angelini (prulifloxacin), Bayer (ciprofloxacin, moxifloxacin), Biocodex (lomefloxacin), Grünenthal

---

<sup>17</sup> Daneman N, Hong L and Redeleier D. A. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* (2015) 5 (11): e010077 doi: 10.1136/bmjopen-2015-010077

<sup>18</sup> Lee C, Lee M, Chen Y, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. *JAMA Intern Med.* 2015;175(11):1839-1847

<sup>19</sup> Pasternak et al. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018;360:k678 | doi: 10.1136/bmj.k678

(pefloxacin), Laboratoires Gerda (flumequine), Mediolanum (rufloxacin), Sanofi (levofloxacin, ofloxacin) and Vianex (norfloxacin) should submit to EMA, within 30 days, comments on a proposal to update the PI with a warning on the increased risk of aortic aneurysm and dissection after intake of fluoroquinolones observed in epidemiological studies, taking into account the newly available evidence. In addition, the MAHs should discuss the need for further risk minimisation measures and communication and make relevant proposals accordingly.

- The PRAC agreed on a LoQ to the study authors to receive additional information and clarifications on the study findings.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

#### 4.3.2. Levothyroxine (NAP); ombitasvir, paritaprevir, ritonavir – VIEKIRAX (CAP)

Applicant(s): AbbVie Deutschland GmbH, various

PRAC Rapporteur: Menno van der Elst

Scope: Signal of interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism

EPITT 18896 – Follow-up to February 2018

##### **Background**

For background information, see [PRAC minutes February 2018](#) and the PRAC recommendation ([EMA/PRAC/59224/2018](#)) published on 05/03/2018 on the EMA website.

Following the PRAC recommendation dated February 2018, further to the conclusion that an interaction between levothyroxine and ritonavir cannot be ruled out based on spontaneous reports and that the interaction should be reflected in the product information of all ritonavir- and levothyroxine-containing medicinal products, the MAH AbbVie Ltd submitted a justification for not submitting the relevant variation recommended by the PRAC, comprising a review of all cases of thyroid abnormality from clinical studies, literature and post marketing reports in patients receiving levothyroxine in association with Viekirax (ombitasvir/paritaprevir/ritonavir), with or without Exviera (dasabuvir sodium). The MAH's justification was assessed by the Rapporteur.

##### **Discussion**

Having considered the justification provided by AbbVie Ltd and in view of the existing wording of the current product information of Viekirax (ombitasvir/paritaprevir/ritonavir) on a potential interaction with levothyroxine, the PRAC agreed that a further update of the product information of Viekirax (ombitasvir/paritaprevir/ritonavir) to reflect the interaction between levothyroxine and ritonavir is not warranted. Therefore the PRAC recommendation adopted in February 2018 for ritonavir is not applicable to Viekirax (ombitasvir/paritaprevir/ritonavir).

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

- The PRAC recommendation adopted in February 2018 is not applicable to Viekirax (ombitasvir/paritaprevir/ritonavir).

4.3.3. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/SDA/091, NAP; abacavir, dolutegravir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/SDA/008; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/SDA/047, NAP; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/SDA/092, NAP; atazanavir - REYATAZ (CAP) - EMEA/H/C/000494/SDA/087; atazanavir, cobicistat - EVOTAZ (CAP) - EMEA/H/C/003904/SDA/004; bictegravir, emtricitabine, tenofovir alafenamide – BIKTARVY (CAP); darunavir - PREZISTA (CAP) - EMEA/H/C/000707/SDA/074; darunavir, cobicistat - REZOLSTA (CAP) - EMEA/H/C/002819/SDA/006; darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - EMEA/H/C/004391/SDA/012; didanosine (NAP); dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/SDA/010; dolutegravir, rilpivirine – JULUCA (CAP); efavirenz - STOCRIN (CAP) - EMEA/H/C/000250/SDA/072.1, SUSTIVA (CAP) - EMEA/H/C/000249/SDA/083.1, NAP; efavirenz, emtricitabine, tenofovir disoproxil - ATRIPLA (CAP) - EMEA/H/C/000797/SDA/043.1; elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide – GENVOYA (CAP); elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil – STRIBILD (CAP); emtricitabine - EMTRIVA (CAP) - EMEA/H/C/000533/SDA/052.1; emtricitabine, rilpivirine, tenofovir alafenamide – ODEFSEY (CAP); emtricitabine, rilpivirine, tenofovir disoproxil – EVIPLERA (CAP); emtricitabine, tenofovir alafenamide – DESCOVY (CAP); emtricitabine, tenofovir disoproxil – TRUVADA (CAP), NAP; enfuvirtide - FUZEON (CAP) - EMEA/H/C/000514/SDA/115; etravirine - INTELENCE (CAP) - EMEA/H/C/000900/SDA/051; fosamprenavir - TELZIR (CAP) - EMEA/H/C/000534/SDA/077; indinavir - CRIXIVAN (CAP) - EMEA/H/C/000128/SDA/040; lamivudine - EPIVIR (CAP) - EMEA/H/C/000107/SDA/054, NAP; lamivudine, tenofovir (NAP); lamivudine, zidovudine - COMBIVIR (CAP) - EMEA/H/C/000190/SDA/040, NAP; lopinavir, ritonavir – KALETRA (CAP); maraviroc - CELSENTRI (CAP) - EMEA/H/C/000811/SDA/042; nevirapine - VIRAMUNE (CAP) - EMEA/H/C/000183/SDA/062; raltegravir - ISENTRESS (CAP) - EMEA/H/C/000860/SDA/058; rilpivirine - EDURANT (CAP) - EMEA/H/C/002264/SDA/027; ritonavir – NORVIR (CAP), NAP; saquinavir - INVIRASE (CAP) - EMEA/H/C/000113/SDA/066; stavudine - ZERIT (CAP) - EMEA/H/C/000110/SDA/065; tenofovir disoproxil - VIREAD (CAP) - EMEA/H/C/000419/SDA/275.1, NAP; tipranavir - APTIVUS (CAP) - EMEA/H/C/000631/SDA/070; zidovudine (NAP)

---

Applicant(s): AbbVie Deutschland GmbH & Co. KG (Kaletra, Norvir), Boehringer Ingelheim International GmbH (Aptivus, Viramune), Bristol-Myers Squibb and Gilead Sciences Ltd. (Atripla), Bristol-Myers Squibb Pharma EEIG (Evotaz, Reyataz, Sustiva, Zerit), Gilead Sciences International Limited (Biktarvy, Viread), Gilead Sciences Ireland UC (Descovy, Emtriva, Eviplera, Genvoya, Odefsey, Stribild, Truvada), Janssen-Cilag International NV (Eduvant, Intelence, Prezista, Rezolsta, Symtuza), Merck Sharp & Dohme B.V. (Isentress, Stocrin), Merck Sharp & Dohme Limited (Crixivan), Roche Registration GmbH (Fuzeon, Invirase), Viiv Healthcare Limited (Celsentri, Combivir, Epivir, Juluca, Kivexa, Telzir, Tivicay, Triumeq, Trizivir, Ziagen), various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of autoimmune hepatitis

EPITT 18956 – Follow-up to March 2018

### Background

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

The MAHs for all originator-antiretroviral medicinal products indicated in the treatment of human immunodeficiency virus (HIV) infection replied to the request for information on the signal of autoimmune hepatitis and the responses were assessed by the Rapporteur.

## Discussion

Having considered the evidence from EudraVigilance and the literature, and the responses from the MAHs, the PRAC agreed that the MAHs of antiretroviral medicinal products against HIV should update their product information to add 'autoimmune hepatitis' in the immune reactivation syndrome description within the special warnings and precautions for use and as an undesirable effect.

## Summary of recommendation(s)

- The MAHs of antiretroviral medicinal products against HIV should submit to EMA and the EU National Competent Authorities as appropriate, within 90 days, a variation to amend the product information<sup>20</sup>.

For the full PRAC recommendation, see [EMA/PRAC/414645/2018](#) published on 06/08/2018 on the EMA website.

### 4.3.4. Hormonal contraceptives:

Chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol<sup>21</sup> (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, norgestimate acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene<sup>22</sup> (NAP); ethinylestradiol, gestodene<sup>23</sup> (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol<sup>24</sup> (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP)

---

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

PRAC Rapporteur: Menno van der Elst

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

EPITT 19143 – Follow-up to March 2018

## Background

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

The study authors of the publication *Morch et al.*, 2017<sup>25</sup> replied to the request for information on the signal related to a known association between hormonal contraceptives

---

<sup>20</sup> Update of SmPC sections 4.4 and 4.8

<sup>21</sup> Contraception indication

<sup>22</sup> All route of administrations except transdermal

<sup>23</sup> Transdermal application

<sup>24</sup> Combination pack

<sup>25</sup> Morch, L. S., Skovlund, C. W., Hannaford, P. C., Iversen, L., Fielding, S. and Lidegaard, O. 2017. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*, 377, 2228-2239



and a small increase in the risk of breast cancer following a recent publication and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence arising from a recent publication on the signal of increased risk of breast cancer with hormonal contraceptives and the additional clarifications on the study findings provided by the study authors, the PRAC concluded that the product information on the known risk of breast cancer with hormonal contraceptives needs to be updated to reflect the new findings from the study by *Morch et al.*

The MAHs for the originator combined hormonal contraceptive-containing products and the MAHs for levonorgestrel intra-uterine system (LNG-IUS) containing products, should submit by 1 August 2018, a wording proposal to update the product information (PI) with a particular focus on the increasing risk of breast cancer with increasing duration of use and the risk of breast cancer being increased with a duration of 1 to less than 5 years of use. Moreover, the MAHs are requested to provide a proposal to include information on the absolute risk of breast cancer in the product information. The MAHs for combined hormonal contraceptives are requested to amend the wording of the current PI.

As the risk estimate for breast cancer with combined hormonal contraceptives in the current product information, which is based on a meta-analysis of 54 epidemiological studies, has been confirmed by the results from *Morch et al.*, the PRAC agreed that this does not need any revision.

## Summary of recommendation(s)

- The MAHs for the originator combined hormonal contraceptive-containing products and the MAHs for LNG-IUS products should submit to EMA, within 20 days, a wording proposal to update the product information<sup>26</sup> with a particular focus on the increasing risk of breast cancer with increasing duration of use and the risk of breast cancer being increased with a duration of 1 to less than 5 years of use as well as a proposal to include information on the absolute risk of breast cancer.
- Additionally, the MAHs for combined hormonal contraceptives are requested to update the existing PI wording accordingly.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

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

---

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of lupus-like syndrome and related terms

EPITT 19098 – Follow-up to April 2018

## Background

---

<sup>26</sup> Update of SmPC sections 4.4. The package leaflet is to be updated accordingly

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

The CHMP Blood Products Working Party (BPWP) replied to the PRAC list of questions on the signal of lupus-like syndrome and related terms and the responses were assessed by the Rapporteur.

### Discussion

Having considered the available evidence, including the views of the BPWP on the signal of lupus like syndrome and related terms (cutaneous lupus erythematosus) as well as the data submitted by the concerned MAHs, the PRAC agreed that the MAHs of intravenous normal human immunoglobulin (IVIgs) containing medical products should update the product information to include cutaneous lupus erythematosus among the undesirable effects with a frequency 'not known'. The MAHs should closely monitor spontaneous cases of 'lupus-like-syndrome' and 'cutaneous lupus erythematosus'. In addition, the MAHs are further advised to investigate anti-Sjogren-antibody (anti-SSA-antibody) levels in affected batches and provide results as part of the case information in the future PSURs.

### Summary of recommendation(s)

- The MAH of IVIgs-containing medical products should submit to EMA, within 90 days, a variation with a view to amend the product information<sup>27</sup>.
- Moreover, the MAHs of IVIgs-containing medical products should closely monitor spontaneous cases of 'lupus-like-syndrome' and 'cutaneous lupus erythematosus'.
- In addition, the MAHs are further advised to investigate anti-Sjogren-antibody (anti-SSA-antibody) levels in affected batches and provide results as part of the case information in future PSURs.

For the full PRAC recommendation, see [EMA/PRAC/414645/2018](#) published on 06/08/2018 on the EMA website.

#### 4.3.6. Hydrochlorothiazide (NAP); Aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)

---

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

PRAC Rapporteur: Kirsti Villikka

Scope: Signal of skin cancer

EPITT 19138 – Follow-up to June 2018

---

<sup>27</sup> Update of SmPC sections 4.4. The package leaflet is to be updated accordingly

## Background

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

The MAHs of originator products containing hydrochlorothiazide (HCTZ) replied to the request to submit a proposal on the updates to the product information on the signal of skin cancer and the responses were assessed by the Rapporteur.

## Discussion

Based on the assessment of the available data sources (i.e. literature, EudraVigilance), the PRAC considered that there was a biologically plausible mechanistic model supporting the increased risk of non-melanoma skin cancer (NMSC) following higher cumulative doses of HCTZ. Therefore, the PRAC agreed that the product information (PI) should be updated to include special warnings and precautions on the observed increased risk of NMSC and to add non-melanoma skin cancer as an undesirable effect with a frequency 'not known'. Therefore, the MAHs of the originator HCTZ-containing products should comment on the proposed PI update. Additionally, the PRAC considered that a direct communication for healthcare professionals (DHPC), at European national level, should be considered. Therefore, the MAHs of originator HCTZ-containing products should make a proposal for a communication plan as well as for a DHPC with a particular focus on defined key elements. Of note, a single consistent message should be delivered.

## Summary of recommendation(s)

- The MAHs of originator HCTZ-containing products should submit to EMA, within 20 days, comments on the proposed PI update.
- In addition, the MAHs of originator HCTZ-containing products should provide a draft communication plan and DHPC for communication at European national level, with a particular focus on defined key elements. Since there are several medicinal products containing the same active substance/combination of substances for which a DHPC is to be issued, the PRAC recommended that a single consistent message is delivered.
- A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 5. Risk management plans (RMPs)

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

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

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

See also Annex I 15.1.

#### 5.1.1. Buprenorphine - EMEA/H/C/004651

Scope: Treatment of opioid dependence within a framework of medical, social and

psychological treatment

#### 5.1.2. Galcanezumab - EMEA/H/C/004648

---

Scope: Prophylaxis of migraine

#### 5.1.3. Influenza vaccine surface antigen inactivated prepared in cell cultures - EMEA/H/C/004814

---

Scope: Prophylaxis of influenza in adults and children from 4 years of age

#### 5.1.4. Mogamulizumab - EMEA/H/C/004232, Orphan

---

Applicant: Kyowa Kirin Limited

Scope: Treatment of cutaneous T-cell lymphoma

#### 5.1.5. Pacritinib - EMEA/H/C/004793, Orphan

---

Applicant: CTI Life Sciences Limited

Scope: Treatment of disease-related splenomegaly and control of symptoms in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) who have thrombocytopenia (platelet counts  $\leq 100,000/\mu\text{L}$ )

#### 5.1.6. Ropeginterferon alfa - EMEA/H/C/004128, Orphan

---

Applicant: AOP Orphan Pharmaceuticals AG

Scope: Treatment of polycythemia vera

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

See also Annex I 15.2.

#### 5.2.1. Ambrisentan - VOLIBRIS (CAP) - EMEA/H/C/000839/II/0055

---

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: Update of the RMP (version 7.6) in order to remove the requirement for educational materials for healthcare professionals given the information provided in the product information and the experience gained in using ambrisentan, as requested by PRAC in the PSUR signal assessment procedure (PSUSA/00000129/201706) concluded in January 2018. Annex II of the product information is updated accordingly. In addition, the MAH took the opportunity to update Annex II to include minor changes including the correction of typographical errors

##### **Background**

Ambrisentan is an orally active, propanoic acid-class, ERA selective for the endothelin A (ETA) receptor. It is indicated, as Volibris, for the treatment of pulmonary arterial

hypertension (PAH) in adult patients of WHO functional class (FC) II to III, including use in combination treatment.

The PRAC is evaluating a type II variation procedure for Volibris, a centrally authorised medicine containing ambrisentan, to update the RMP to reflect changes on the additional risk minimisation measures, including the distribution of patient alert cards focused on the important identified risk of 'hepatotoxicity' and 'teratogenicity', as well as the proposed removal of the requirement for educational materials for healthcare professionals and male partners of women of child-bearing potential. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation.

#### **Summary of advice**

- The RMP for Volibris (ambrisentan) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 7.6 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC supported the discontinuation of the requirement for educational material as it was considered that healthcare professionals (HCP) specialised in PAH are well trained and aware of the relevant risk management. In addition, some of the risk minimisation measures in place have become part of standard clinical practice. Nevertheless, the MAH should ensure the ongoing provision of educational materials targeting patients (i.e. patient alert card) focused on the important identified risks of 'hepatotoxicity' and 'teratogenicity'.

#### **5.2.2. Infliximab - REMICADE (CAP) - EMEA/H/C/000240/II/0214**

---

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 17.0) and Annex II-D of the product information to remove the educational material for healthcare professionals. In addition, the MAH took the opportunity to update the package leaflet with some missing warnings and adverse drug reactions (ADR) already reflected in the SmPC, as requested by CHMP, and to introduce some minor quality review of documents (QRD)-related changes

#### **Background**

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to tumour necrosis factor alfa (TNF $\alpha$ ). It is indicated, as Remicade, for the treatment of rheumatoid arthritis, psoriatic arthritis, Crohn's disease, in adults and children from 6 years, ulcerative colitis, in adults and children from 6 years, ankylosing spondylitis, and plaque psoriasis.

The PRAC is evaluating a type II variation procedure, to update the RMP to reflect changes to the additional risk minimisation measures, including a proposal from the MAH to remove the requirement for educational materials for healthcare professionals following the results of the latest survey conducted by the MAH on risk awareness of prescribers, as well as to reflect the continuous distribution of patient cards to remind patients of the most important risks and their symptoms, as well as the importance of informing caregivers of their medication.

The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

#### **Summary of advice**

- The RMP for Remicade (infliximab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 17.0 and satisfactory responses to the request for supplementary information (RSI) are submitted.
- The PRAC supported the discontinuation of the requirement for educational material as the awareness and knowledge of prescribers on the safety profile of Remicade (infliximab) was considered high. In addition, the PRAC acknowledged that risk management for Remicade (infliximab) has been integrated in guidelines and recommendations over the years, and is now part of routine clinical practice. Nevertheless, the MAH should ensure the provision of educational materials targeting patients (i.e. patient reminder card).

#### **5.2.3. Oseltamivir - TAMIFLU (CAP) - EMEA/H/C/000402/II/0133**

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Kirsti Villikka

Scope: Update of the RMP (version 16) to discontinue the guided questionnaires (GQ) for neurological and psychiatric adverse events (NPAE), hepatobiliary disorders and hypothermia

#### **Background**

Oseltamivir phosphate is a pro-drug of the active metabolite oseltamivir carboxylate which is a selective inhibitor of influenza virus neuraminidase enzymes. Oseltamivir, as Tamiflu, is indicated in adults and children including full term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. It is also indicated for post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community under certain conditions as well as for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

The PRAC is evaluating a type II variation procedure for Tamiflu, a centrally authorised medicine containing oseltamivir, to update the RMP to reflect the discontinuation of the guided questionnaires (GQ) to enhance data collection for neuro-psychiatric events (NPAEs), hepatobiliary disorders, including any adverse events reported in patients with underlying liver disorders, and hypothermia. The RMP is also revised in line with revision 2 of GVP module V on 'Risk management systems'. Indeed, several safety concerns are removed since they no longer meet the definition of important safety concern i.e., they do not require additional pharmacovigilance activities, additional risk minimisation activities or routine risk minimisation activities recommending specific clinical measures to address such risks as they can be managed through the means of the product information. 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 16.0 for Tamiflu (oseltamivir) in the context of the variation procedure under evaluation by the CHMP is acceptable.
- The PRAC supported the discontinuation of the GQ since it did not contribute to further characterize the risks of 'NPAEs', 'hepatobiliary disorders' and 'hypothermia' after the available medical evidence collected over 18 years of post-marketing experience. Nevertheless, the MAH should continue to closely monitor these risks.

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

See also Annex I 15.3.

#### 5.3.1. Nusinersen - SPINRAZA (CAP) - EMEA/H/C/004312/II/0004, Orphan

---

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.8 of the SmPC to include new safety information related to hydrocephalus. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to correct some typographical errors in section 5.1 of the SmPC

#### Background

Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). It is indicated, as Spinraza, for the treatment of 5q spinal muscular atrophy (SMA).

The CHMP is evaluating a variation application for Spinraza, a centrally authorised product containing nusinersen, consisting of an update of the product information proposing to add 'hydrocephalus' as an undesirable effect and a warning requiring a ventriculo-peritoneal shunt procedure, following the development in a few infants of communicating hydrocephalus without signs of meningitis or bleeding. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this procedure. For further background, see [PRAC minutes February 2018](#), [PRAC minutes April 2018](#) and [PRAC minutes June 2018](#).

#### Summary of advice

- The RMP for Spinraza (nusinersen) version 10 in the context of the variation procedure under evaluation by the CHMP is considered acceptable.
- The PRAC agreed on the content of the direct health professional communication (DHPC) and the communication plan to inform physicians and investigators at the remaining trial sites on the cases of 'hydrocephalus' in infants and adults with key elements in line with the agreed changes to the product information.



## 6. Periodic safety update reports (PSURs)

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

See also Annex I 16.1.

#### 6.1.1. Concentrate of proteolytic enzymes enriched in bromelain - NEXOBRID (CAP) - PSUSA/00010028/201712

---

Applicant: MediWound Germany GmbH

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Concentrate of proteolytic enzymes enriched in bromelain is an enzyme mixture dissolving burn wound eschar and is indicated as NexoBrid for removal of eschar in adults with deep partial- and full-thickness thermal burns.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of NexoBrid, a centrally authorised medicine containing a concentrate of proteolytic enzymes enriched in bromelain, and issued a recommendation on its marketing authorisation(s).

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the method of administration to specify that acute wound areas such as lacerations or escharotomy incisions should be protected by a layer of a sterile fat-containing ointment or fat-containing dressing (e.g. petrolatum gauze) to prevent possible irritation of abraded skin by inadvertent contact with NexoBrid (concentrate of proteolytic enzymes enriched in bromelain). 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.

#### 6.1.2. Ingenol mebutate - PICATO (CAP) - PSUSA/00010035/201801

---

Applicant: LEO Laboratories Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

##### **Background**

---

<sup>28</sup> Update of SmPC section 4.2. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Ingenol mebutate has shown in *in vivo* and *in vitro* models a dual mechanism of action for the effects of induction of local lesion cell death and for promoting an inflammatory response characterised by local production of pro-inflammatory cytokines and chemokines and infiltration of immunocompetent cells. Ingenol mebutate, as Picato, is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

The PRAC is currently reviewing the benefit-risk balance of Picato, a centrally authorised medicine containing ingenol mebutate, in the framework of the assessment of a PSUR single assessment (PSUSA) procedure due for PRAC recommendation at the September 2018 PRAC meeting.

### Summary of conclusions

- The PRAC Rapporteur presented the preliminary assessment of the currently ongoing PSUSA procedure, which is due to complete at the following PRAC meeting. To this effect, the PRAC requested supplementary information from the MAH. Further discussion and adoption of a recommendation is planned at the September 2018 PRAC meeting.

### 6.1.3. Nivolumab - OPDIVO (CAP) - PSUSA/00010379/201801

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

### Background

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. It is indicated, as Opdivo, in monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. It is also indicated as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults, for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, and for the treatment of squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy as well as for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

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

### Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Opdivo (nivolumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'pericardial disorders' as an undesirable effect with frequency 'uncommon' in monotherapy and with

frequency 'not known' in combination with ipilimumab. Therefore the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.

- The MAH should submit to EMA, within 90 days, detailed analyses of cases of 'aseptic meningitis' and 'anaemia', including cases of 'haemolytic anaemia' and 'autoimmune anaemia' and propose to update the product information as applicable.
- In the next PSUR, the MAH should provide cumulative reviews of cases of 'coronary artery disorders', 'haemophagocytic histiocytosis' and 'recall phenomenon' as well as a comprehensive review of cases of 'systemic lupus erythematosus', assessing the causality of nivolumab in these reactions. In addition, the MAH should include an analysis of available biomarkers suitable to monitor patients in ongoing trials to prove hyperprogression.

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. Ponatinib - ICLUSIG (CAP) - PSUSA/00010128/201712

---

Applicant: Incyte Biosciences Distribution B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ponatinib is a potent pan BCR<sup>30</sup>-ABL<sup>31</sup> inhibitor indicated, as Iclusig, in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I<sup>32</sup> mutation. It is also indicated in adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Iclusig (ponatinib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'posterior reversible encephalopathy syndrome (PRES)' as an undesirable effect with frequency 'uncommon' and a warning that treatment with Iclusig (ponatinib) should be interrupted if PRES is

---

<sup>29</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>30</sup> breakpoint cluster region protein

<sup>31</sup> Abelson

<sup>32</sup> Amino acid substitution at position 315 in BCR-ABL1

diagnosed and treatment resumed only once the event is resolved. Therefore the current terms of the marketing authorisation(s) should be varied<sup>33</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.

#### 6.1.5. Secukinumab - COSENTYX (CAP) - PSUSA/00010341/201712

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

##### **Background**

Secukinumab is a fully human IgG1/ $\kappa$ <sup>34</sup> monoclonal antibody that selectively binds to and neutralises the pro-inflammatory cytokine interleukin-17A (IL-17A). It is indicated, as Cosentyx, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy as well as for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. It is also indicated alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cosentyx (secukinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and infections. Therefore the current terms of the marketing authorisation(s) should be varied<sup>35</sup>.
- In the next PSUR, the MAH should provide a detailed review of clinical data and spontaneous reports on patient with inflammatory bowel disease and propose to update the product information as applicable.
- The MAH should submit to EMA within the next regulatory opportunity an updated RMP to address the changes made in the product information on the important potential risk of 'Crohn's disease' to 'inflammatory bowel disease (Crohn's disease and ulcerative colitis)'.

---

<sup>33</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>34</sup> Immunoglobulin G, subclass 1,  $\kappa$  light chain

<sup>35</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

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. Ticagrelor - BRILIQUE (CAP) - PSUSA/00002948/201712

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ticagrelor is a cyclopentyltriazolopyrimidine (CPTP) and is indicated, as Brilique, in co-administration with acetylsalicylic acid (ASA) for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Brilique (ticagrelor) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on discontinuation of Brilique (ticagrelor) prior to surgery. Therefore the current terms of the marketing authorisation(s) should be varied<sup>36</sup>.
- In the next PSUR, the MAH should include a review on off-label reports of patients using Brilique (ticagrelor) longer than 12 months, comparing this to adverse events reported for patients using Brilique (ticagrelor) for 12 months. In addition, the MAH should provide a cumulative review of cases of 'sleep apnoea syndrome', including cases with positive dechallenge and/or positive rechallenge together with a proposal to update the product information as applicable.

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

#### 6.1.7. Ustekinumab - STELARA (CAP) - PSUSA/00003085/201712

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

##### **Background**

---

<sup>36</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

Ustekinumab is a fully human IgG1κ<sup>37</sup> monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. It is indicated, as Stelara, for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor alfa (TNFα) antagonist or have medical contraindications to such therapies; for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A); for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Finally, it is indicated alone or in combination with MTX for the treatment of active psoriatic arthritis (PsA) in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Stelara (ustekinumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to remove the additional risk minimisation measures consisting of educational materials for healthcare professionals (HCPs) and patients from Annex II on 'conditions or restrictions with regards to the safe and effective use of the medicinal product' as the relevant safety information of the educational materials is contained in the product information and the management of risks has been integrated into routine clinical practice. Therefore the current terms of the marketing authorisation(s) should be varied<sup>38</sup>.
- The MAH should submit to EMA, within 90 days, an updated RMP to remove the educational materials for HCPs and patients as additional risk minimisation measures in line with the changes made in Annex II on 'conditions or restrictions with regards to the safe and effective use of the medicinal product'.
- In the next PSUR, the MAH should submit a cumulative review of cases of 'vasculitis' and 'non-thrombotic purpura'.

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

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

See also Annex I 16.2.

---

<sup>37</sup> Immunoglobulin G, subclass 1, κ light chain

<sup>38</sup> Update of SmPC Annex II section D. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

#### 6.2.1. Lutetium (<sup>177</sup>Lu) chloride - ENDOLUCINBETA (CAP), LUMARK (CAP); NAP - PSUSA/00010391/201712

---

Applicants: ITG Isotope Technologies Garching GmbH (EndolucinBeta), I.D.B. Holland B.V. (LuMark), various

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

##### **Background**

Lutetium chloride is a radiopharmaceutical precursor indicated for the radiolabelling of carrier molecules specifically developed and authorised for radiolabelling with this radionuclide.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lutetium chloride-containing medicinal products in the approved indications remains unchanged.
- Nevertheless, the product information should be updated to include warnings on 'hepatotoxicity', and, 'hormone release syndromes'. Furthermore, the product information should be updated to add 'carcinoid crisis' as an undesirable effect with frequency 'not known' as well as 'nausea' and 'vomiting' as undesirable effects with frequency 'very common'. Therefore the current terms of the marketing authorisations should be varied<sup>39</sup>.
- In the next PSUR, the MAH should provide a cumulative review of cases of 'radiation-induced gastrointestinal toxicity'.
- MAH(s) with an RMP in place for their medicinal product(s) should submit to EMA, within 180 days, an updated RMP to include 'hepatotoxicity' as an important potential risk including a discussion regarding appropriate pharmacovigilance measures.

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

See also Annex I 16.3.

#### 6.3.1. Abciximab (NAP) - PSUSA/00000014/201711

---

Applicant(s): various

---

<sup>39</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



PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

### **Background**

Abciximab is an inhibitor of platelet aggregation indicated as an adjunct to heparin and acetylsalicylic acid for the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention and for the short-term reduction of the risk of myocardial infarction in patients with unstable angina under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of abciximab-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the PRAC considered that cases of 'delayed thrombocytopenia' needed to be further assessed. Further consideration is to be given at the level of the CMDh.

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

## **6.3.2. Furosemide, spironolactone (NAP) - PSUSA/00001493/201712**

---

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

### **Background**

Furosemide is a loop diuretic and spironolactone is an aldosterone antagonist. In combination, furosemide/spironolactone is indicated for the treatment of ascites in patients with liver diseases, for the treatment of oedema and congestion of the lungs due to cardiac insufficiency, and oedema in patients with nephrotic syndrome (NS). It is also indicated for the treatment of hypertension under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of furosemide/spironolactone-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.

- In the next PSUR, the MAH(s) should provide a characterisation of the risks of 'osteomalacia', 'decreased bone mineral density' (BMD) and 'osteoporotic fractures'.

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

### 6.3.3. Hydroxycarbamide<sup>40</sup> (NAP) - PSUSA/00009182/201712

---

Applicant(s): various

PRAC Lead: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### Background

Hydroxycarbamide is an antineoplastic agent indicated for the treatment of chronic myelocytic leukaemia (CML) under certain conditions, and other myeloproliferative disorders, including essential thrombocythaemia (ET), polycythaemia vera (PCV) and idiopathic myelofibrosis. It is also indicated for the treatment of primary squamous cell carcinoma (or epidermoid) of the head and neck, excluding the lip, in combination with 5-fluorouracil and radiotherapy and sickle cell disease (SCD).

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of hydroxycarbamide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on use in patients with respiratory symptoms and to include 'interstitial lung disease' as an undesirable effect with frequency 'not known'. In addition, a warning on 'skin cancer' should be added. Therefore the current terms of the marketing authorisation(s) should be varied<sup>41</sup>.
- In the next PSUR, the MAHs should provide cumulative analyses of cases of 'hyperkalaemia' and of 'opportunistic infections'. In addition, the MAHs should provide a detailed assessment of all new cases of 'pyoderma gangrenosum' and cases of 'melanoma'. Lastly, the MAHs should provide all available results of two studies<sup>42 43</sup> on the use of hydroxycarbamide in myeloproliferative disorders (MPD) and discuss their relevance for the safety issue of secondary malignancy.

---

<sup>40</sup> Non-centrally authorised products only

<sup>41</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>42</sup> Randomized trial of pegylated interferon alfa-2a versus hydroxyurea in PV and ET

<sup>43</sup> Study of low dose interferon alpha versus hydroxyurea in treatment of chronic myeloid neoplasms (DALIAH)

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. Iron<sup>44</sup> (NAP) - PSUSA/00010236/201801

---

Applicant(s): various

PRAC Lead: Zane Neikena

Scope: Evaluation of a PSUSA procedure

##### **Background**

Iron complexes include iron sucrose, iron carboxymaltose, iron (III) isomaltoside and sodium ferric gluconate and iron dextran for parenteral preparations. They are indicated for intravenous (IV) iron supplementation to correct iron deficiency and to replenish iron stores.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of iron complexes-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'influenza like illness' as an undesirable effect with a product-specific frequency, as applicable. Therefore the current terms of the marketing authorisation(s) should be varied<sup>45</sup>.
- In the next PSUR, all MAHs should include a detailed review of cases of 'hypersensitivity reactions' from the ongoing PASS imposed as an outcome of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013 ([EMA/H/A31/1322](#)) and discuss the effectiveness of the risk minimisation measures in place. Summaries of annual cumulative reports on hypersensitivity should be provided in a consistent format to allow the data to be considered in a comparable way. In addition, the MAHs should include a cumulative review of cases of 'osteomalacia' with a proposal to update the product information as applicable. Lastly, the MAHs should closely monitor cases of 'arrhythmias' and 'thromboembolic events' with a proposal to update the product information as applicable.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. However, the PRAC considered that PSURs for medicinal products containing iron dextran for parenteral preparations should be assessed in a separate PSUSA procedure with the same data lock point (DLP) and frequency. Therefore the EURD list should be updated accordingly.

---

<sup>44</sup> Parenteral preparations only

<sup>45</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

### 6.3.5. Lamotrigine (NAP) - PSUSA/00001825/201711

---

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### Background

Lamotrigine is a phenyltriazine derivative indicated for the prevention of depressive episodes in patients with bipolar I disorder (BP-I) and for the treatment of epilepsy under certain conditions.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of lamotrigine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on 'haemophagocytic lymphohistiocytosis' (HLH) and 'Brugada-type ECG<sup>46</sup>', and to add 'HLH' and 'hypogammaglobulinaemia' as undesirable effects with a frequency 'very rare'. Lastly, the product information should be updated to refine the clinical particulars during pregnancy and lactation. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>47</sup>.
- In the next PSUR, the MAHs should provide a cumulative analysis of cases of 'memory impairment' associated with lamotrigine, and propose amendments to the product information, as applicable. In addition, the MAH GlaxoSmithKline should provide a cumulative analysis of cases of 'eosinophilic pneumonia'.

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

### 6.3.6. Mizolastine (NAP) - PSUSA/00002078/201711

---

Applicant(s): various

PRAC Lead: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### Background

Mizolastine is a benzimidazole derivative indicated for the symptomatic relief of seasonal allergic rhinoconjunctivitis (hay fever), perennial allergic rhinoconjunctivitis and urticaria in adults and children of 12 years of age and older.

---

<sup>46</sup> Electrocardiogram

<sup>47</sup> Update of SmPC sections 4.4, 4.6 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of mizolastine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'vomiting' as an undesirable effect with frequency 'not known'. Therefore the current terms of the marketing authorisation(s) should be varied<sup>48</sup>.

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

#### **6.3.7. Paroxetine (NAP) - PSUSA/00002319/201712**

---

Applicant(s): various

PRAC Lead: Sabine Straus

Scope: Evaluation of a PSUSA procedure

#### **Background**

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) indicated for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder with and without agoraphobia, social anxiety disorder (SAD), generalised anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). Paroxetine controlled-release (CR) formulation is indicated for MDD, premenstrual dysphoric disorder (PMDD), panic disorder and social anxiety disorder/social phobia.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of paroxetine-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include 'bruxism' as an undesirable effect with frequency 'not known'. Therefore the current terms of the marketing authorisation(s) should be varied<sup>49</sup>.
- The PRAC considered that the signal on 'drug reaction with eosinophilia and systemic symptoms (DRESS)' needed to be further assessed. Further consideration is to be given at the level of the CMDh.

---

<sup>48</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>49</sup> Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

- With regard to persistent sexual dysfunction after discontinuation of paroxetine, the PRAC considered that this issue should be further investigated in September 2018 in the context of a separate review.

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

#### 6.3.8. Phenylephrine, tropicamide (NAP) - PSUSA/00010430/201711

---

Applicant(s): various

PRAC Lead: Doris Stenver

Scope: Evaluation of a PSUSA procedure

##### **Background**

Phenylephrine is an alpha sympathomimetic and tropicamide is an anticholinergic. In combination, phenylephrine/tropicamide is indicated for mydriasis for the examination of the optic fundus, for iritis, for iridocyclitis, for uveitis as well as for diagnostic purposes.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of phenylephrine/tropicamide-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- Nevertheless, the PRAC considered that 'systemic adverse reactions' associated with ophthalmic use of medicinal products containing phenylephrine in the paediatric population needed to be further assessed. Further consideration is to be given at the level of the CMDh.

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

#### 6.3.9. Propofol (NAP) - PSUSA/00002555/201711

---

Applicant(s): various

PRAC Lead: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

##### **Background**

Propofol is an intravenous (IV) 2, 6-diisopropylphenol medicinal compound indicated for the induction and maintenance of general anaesthesia. It is also indicated for sedation of ventilated patients receiving intensive care, for sedation in adults undergoing surgical and/or

diagnostic procedures and for short term sedation for diagnostic and therapeutic procedures in children.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of propofol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to strengthen the warning on propofol infusion syndrome (PRIS). Therefore the current terms of the marketing authorisation(s) should be varied<sup>50</sup>.
- In the next PSUR, the MAHs should closely monitor cases of 'anaphylaxis including hypersensitivity in patients with food allergy', cases of 'anticholinergic syndrome including delirium, agitation and hallucination', as well as cases of 'PRIS' following a scientific publication by *Bledsoe et al.*<sup>51</sup> suggesting valproic acid as a triggering factor for the development of PRIS.

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

#### **6.3.10. Rosuvastatin (NAP) - PSUSA/00002664/201711**

---

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Rosuvastatin is an inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase indicated for the treatment of hypercholesterolaemia and dyslipidaemia in adults, adolescents and children aged 6 years or older, and for the prevention of cardiovascular events.

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

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

---

<sup>50</sup> Update of SmPC section 4.4. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>51</sup> Bledsoe KA, Hedrick JN, Corbett SM, Charlton NP. Valproic acid as a triggering factor for propofol infusion syndrome in critically ill patients. *Neurocritical Care* 21 (Suppl. 1): S218, No. 1, Sep 2014



- Based on the review of the data on safety and efficacy, the benefit-risk balance of rosuvastatin-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include the interaction of rosuvastatin with regorafenib and protease inhibitors. Therefore the current terms of the marketing authorisation(s) should be varied<sup>52</sup>.
- In the next PSUR, the MAHs should provide detailed reviews of cases of 'skin reactions', including photosensitivity reactions and eczema, cases of 'aphasia' and cases of 'vasculitis', and discuss the need for update of the product information, as applicable.
- Cases of 'systemic lupus erythematosus/lupus erythematosus/lupus-like syndrome' and 'muscle rupture/torn muscle' needed to be further assessed. Further consideration is to be given at the level of the CMDh.
- The PRAC also considered that it is relevant to introduce the drug interaction with the protease inhibitors regorafenib, velpatasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, grazoprevir/elbasvir, and glecaprevir/pibrentasvir in the product information of medicinal products containing rosuvastatin in fixed dose combinations. Further consideration is to be given at the level of the CMDh.

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

#### 6.3.11. Tapentadol (NAP) - PSUSA/00002849/201711

---

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

##### **Background**

Tapentadol is a centrally acting synthetic analgesic indicated for the relief of moderate to severe acute pain, and for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of tapentadol-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the warning on 'risk of seizures' in patients taking tapentadol with concomitant medication decreasing the

---

<sup>52</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

seizure threshold as it may increase the seizure risk. Therefore the current terms of the marketing authorisation(s) should be varied<sup>53</sup>.

- In the next PSUR, the MAHs should provide cumulative analyses of cases of 'epilepsy' and 'seizures', and discuss the need for update of the product information, as applicable.

The frequency of PSUR submission should be revised from three yearly to yearly and the next PSUR should be submitted to the EMA within 70 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

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

See Annex I 16.4.

# 7. Post-authorisation safety studies (PASS)

## 7.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>54</sup>

See also annex I 17.1.

### 7.1.1. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064

Applicant: Medice Arzneimittel Pütter GmbH & Co. KG (Medikinet Retard)

PRAC Rapporteur: Martin Huber

Scope: Protocol for a multicentre, observational, prospective PASS to evaluate the safety concerns of long-term cardiovascular and psychiatric risks within the adult attention deficit/hyperactivity disorder (ADHD) population taking Medikinet Retard (methylphenidate hydrochloride) according to normal standard clinical practice

#### Background

Methylphenidate hydrochloride is a centrally acting sympathomimetic indicated for attention-deficit hyperactivity disorder (ADHD) in children aged 6 years of age and over under certain conditions. In 2017 the MAH of Medikinet Retard (methylphenidate hydrochloride) submitted a type II variation (DE/H/0690/004-010/II/043/G) applying for the addition of a new therapeutic indication for use in adults. Due to disagreement between EU Member States, a CMDh referral procedure was triggered. Further to the conclusion of the referral procedure at CMDh in November 2017 (see [CMDh meeting November 2017](#)), the MAH was required to conduct a non-interventional PASS category 1 in adult ADHD patients (aged  $\geq 18$  years) to generate long-term safety data on cardiovascular and psychiatric adverse events in the adult ADHD population. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, MEDICE Arzneimittel Pütter GmbH & Co. KG submitted on 03/05/2018 a PASS protocol version 1.0 dated 28 March 2018 to the EMA for Medikinet retard (methylphenidate hydrochloride). The evaluation procedure started on 14/05/2018. The protocol for the PASS study entitled 'a multicentre, observational, prospective, PASS to evaluate the long-term

<sup>53</sup> Update of SmPC sections 4.4 and 4.5. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>54</sup> In accordance with Article 107n of Directive 2001/83/EC

cardiovascular and psychiatric safety profile of Medikinet Retard in adult patients with attention deficit/hyperactivity disorder', was presented for review by the PRAC.

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

- The PRAC, having considered the protocol version 1.0 in accordance with Article 107n of Directive 2001/83/EC, objected to the protocol for the above listed medicinal product, as the Committee considered that the design of the study did not fulfil the study objectives.
- The PRAC recommended that the MAH revises the protocol to propose a new study design based on databases as a single-arm cohort study design is not considered acceptable, with the addition of a suitable comparator to assess whether adverse outcomes occur more frequently or to a greater severity as a result of the exposure to methylphenidate, and replacement of the proposed primary endpoint by an endpoint with higher clinical relevance. Moreover, the MAH should take into account, upon drafting the revised study protocol, the studies by *Schelleman et al.*<sup>55</sup> and *Habel et al.*<sup>56</sup> that were conducted in adult patients based on U.S. health claims. Finally, it is suggested to first agree the study protocol and then agree the statistical analysis plan (SAP) as part of this PASS evaluation procedure implying that the study will only start after regulatory agreement on both PASS and SAP.
- The MAH should submit a revised PASS protocol within 90 days to the EMA. A 60 days-assessment timetable will be applied.

## **7.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>57</sup>**

See Annex I 17.2.

## **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>58</sup>**

### **7.3.1. Domperidone (NAP) - EMEA/H/N/PSR/J/0010**

---

Applicant(s): Janssen Pharmaceutical Companies of Johnson & Johnson (consortium)

PRAC Rapporteur: Caroline Laborde

Scope: Results for a PASS assessing the effectiveness of the risk minimisation measures of domperidone to characterise prescribers' knowledge, understanding and extent of awareness regarding new safety information for domperidone following the change in SmPC and the distribution of a direct healthcare professional communication (DHPC), as imposed in the conclusions of the referral procedure under Article 31 of Directive 2001/83/EC concluded in 2013, as per the request for supplementary information (RSI) adopted by PRAC in March 2018

#### **Background**

---

<sup>55</sup> Methylphenidate and risk of serious cardiovascular events in adults. *Am J Psychiatry*. 2012 Feb; 169(2): 178-85

<sup>56</sup> ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA*. 2011 Dec 28; 306(24): 2673-83

<sup>57</sup> In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

<sup>58</sup> In accordance with Article 107p-q of Directive 2001/83/EC

Domperidone is a D<sub>2</sub>-receptor antagonist indicated for the relief of the symptoms of nausea and vomiting. In line with the conclusions dated 2014 of the referral procedure under Article 31 of Directive 2001/83/EC ([EMEA/H/A-31/1365](#)) conducted by the PRAC for domperidone-containing medicines, MAHs were required as a condition to the marketing authorisations ([Annex IV](#)) to conduct a drug utilisation study (DUS) in several Member States to assess the effectiveness of the agreed risk minimisation measures and to monitor off-label use. The study protocol was to be submitted within 3 months after the European Commission decision. In January 2016, the PRAC endorsed the PASS (DUS) protocol version 3 (dated 12 October 2015) submitted by the MAH Janssen Research and Development on behalf of a group of MAHs (the Domperidone Collaboration Study Group). For further background, see [PRAC minutes March 2014](#), [PRAC minutes April 2015](#), [PRAC minutes September 2015](#), [PRAC minutes January 2016](#), [PRAC minutes November 2017 \(23-26 October 2017\)](#) and [PRAC minutes March 2018](#).

The final study report was submitted to EMA by the MAH Janssen Research and Development on behalf of a group of MAHs (Domperidone Collaboration Study Group) on 29 August 2017. The PRAC discussed the final study results.

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

- Based on the review of the final report of the non-interventional PASS entitled 'a post-authorisation safety study (PASS) to assess the effectiveness of the risk minimisation measures of domperidone–physician survey', as well as the MAH's responses to the request for supplementary information (RSI), the PRAC considered that the benefit-risk balance of medicinal products containing the active substance domperidone remains unchanged and recommended on 21/09/2018, by written procedure, the maintenance of the terms of the Marketing Authorisation(s) for the medicinal products containing domperidone.

#### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>59</sup>**

See Annex I 17.4.

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

See Annex I 17.5.

#### **7.6. Others**

See Annex I 17.6.

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

None

---

<sup>59</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

## 7.8. Ongoing Scientific Advice

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

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

None

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

## 8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

## 8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

## 8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

### 8.3.1. Dimethyl fumarate - TECFIDERA (CAP) - EMEA/H/C/002601/R/0053 (without RMP)

Applicant: Biogen Idec Ltd

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

#### Background

Tecfidera is a medicine centrally authorised in 2014 containing dimethyl fumarate (DMF), a methylester of fumaric acid. Tecfidera (dimethyl fumarate) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis.

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

#### Summary of advice

- Based on the review of the available pharmacovigilance data for Tecfidera (dimethyl fumarate) and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds relating to the need for further characterisation of the important identified risks of 'decrease in leukocyte and lymphocyte counts', 'progressive multifocal leukoencephalopathy (PML)' and 'herpes zoster'.
- The PRAC concluded that no relevant safety concerns had arisen from the assessment of this first renewal procedure. In addition, the MAH is requested to continue close monitoring of the safety issues 'PML' and 'herpes zoster' and to review these topics

within the next PSUR, including a thorough review of cumulative cases from EudraVigilance, also with regard to an association with a decrease in lymphocyte counts. The MAH should discuss whether further risk minimisation measures are warranted for any of the risks, e.g. more frequent monitoring of complete blood count (CBC) or further warnings in the product information (PI). Results from currently ongoing studies investigating the effect of DMF on lymphocytes should also be taken into account. In addition to a review of the total number of herpes zoster cases, severe cases should also be reviewed separately, including disseminated forms of herpes zoster, manifestations on the face and cases with sequelae. In order to enable assessment of these issues in a timely manner, the PRAC advised to reduce the PSUR frequency to yearly.

## **9. Product related pharmacovigilance inspections**

### **9.1. List of planned pharmacovigilance inspections**

#### **9.1.1. Risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders connected with human centrally authorised products**

---

Scope: Pharmacovigilance inspection programme 2018-2021 (first revision for 2018)

The PRAC agreed the list of planned pharmacovigilance inspections for 2018-2021, proposed by the Pharmacovigilance Inspector Working Group ([PhV IWG](#)) according to a risk-based approach. This list is subsequently due for adoption at CHMP. For further background, see [PRAC minutes December 2017](#).

Post-meeting note: On 26 July 2018, the CHMP adopted the pharmacovigilance inspection programme 2018-2021, first revision.

### **9.2. Ongoing or concluded pharmacovigilance inspections**

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

### **9.3. Others**

None

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

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

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

---

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Julie Williams

Scope: PRAC consultation on a variation to update sections 4.6 and 5.3 of the SmPC as requested in the conclusions of the PSUSA procedure (PSUSA/00010373/201703) adopted

by PRAC at its November 2017 meeting in order to include revised safety information about pregnancy and risk of congenital malformations or foetal toxicity. The package leaflet is updated accordingly

## Background

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

Following the review of the latest PSUR for raltegravir-containing products (procedure PSUSA/00010373/201703, see [PRAC minutes November 2017 \(23-26 October 2017\)](#)), the MAH was requested to provide additional data and/or additional analysis to demonstrate the safe use of raltegravir in pregnancy and the lack of potential for foetotoxicity and to update the product information accordingly via a type II variation. This variation proposing to update the product information is under evaluation at the CHMP (EMA/H/C/000860/II/0073). In order to support the proposed product information changes, the MAH provided and reviewed published scientific literature to support an opinion that results from previously conducted animal studies do not indicate foetotoxicity. The MAH also provided clinical safety information in the form of an analysis of a recent Antiretroviral Pregnancy Registry (APR) interim report, referenced, reports from the company's pharmacovigilance database, and one literature article. Following a request for supplementary information, further non-clinical and clinical information was provided by the MAH. The MAH proposed to remove the statement relating to reproductive toxicity from the product information (PI) section on pregnancy and lactation with a rationale based on reaching the threshold required by EU guidance of at least 300 first trimester prospective pregnancies. The PRAC was requested to provide advice to CHMP on this variation procedure.

## Summary of advice

- The PRAC discussed the MAH's proposal to remove the statement relating to reproductive toxicity from the PI section on pregnancy and lactation and noted the concerns regarding the exposure-response relationship in non-clinical data as well as that supernumerary ribs (SNRs) observed in non-clinical studies appear to be a direct drug effect in the embryo due to absence of maternal toxicity in a specific repro/development study with narrow exposure margins.
- Overall, considering the totality of the available non-clinical and clinical data and taking into account a recent signal of neural tube defects associated with another integrase inhibitor following exposure prior to or at the time of conception, the PRAC acknowledged that the data were not sufficiently reassuring to support updates at this stage. In particular, the PRAC supported the Rapporteur's proposal to keep the sentence stating that 'studies in animals have shown reproductive toxicity' in the PI section on pregnancy and lactation. Furthermore, the PRAC noted that the number of exposed pregnancies was relatively low and it was likely that the number of pregnancies exposed prior to or at the time of conception was even lower. Therefore, the PRAC advised a precautionary approach to be maintained and that advice in the PI of all Isentress (raltegravir) formulations with regards to use during pregnancy should continue to state that use is not recommended.



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

None

## 10.3. Other requests

None

## 10.4. Scientific Advice – PRAC consultation

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

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

## 11.1. Safety related variations of the marketing authorisation

### 11.1.1. Dienogest, estradiol valerate (NAP) - NL/H/1230/001/II/034

Applicant(s): Bayer BV (Qlaira)

PRAC Lead: Menno van der Elst

Scope: PRAC consultation on a national variation to assess the final results of an imposed cohort study INAS-SCORE, an 'international active surveillance study, safety of contraceptives: role of estrogens' conducted in the US and Europe and the proposed amendments to the product information on the risk of venous thromboembolism (VTE), on request of the Netherlands (Reference Member State)

### Background

Qlaira, a combined oral contraceptive (COC) containing estradiol valerate (EV) as an oestrogen and dienogest (DNG) as a progesterone component is used for contraception and the treatment of heavy menstrual bleeding in women without organ pathology who desire oral contraception.

Further to the submission by the MAH of the final study report II of INAS-SCORE, performed to assess the risk of venous thromboembolism (VTE) associated with Qlaira (DNG/EV) and the subsequent MAH's proposal to update the product information (PI)<sup>60</sup>, the Netherlands requested PRAC advice in February 2018, on its assessment of the final results of the INAS-SCORE study and the MAH's proposals for updating the product information to include the findings of this study. It was considered that further clarifications on the study results were needed before any conclusions could be drawn regarding the risk of VTE associated with Qlaira (DNG/EV). As a result, the PRAC supported addressing a list of questions (LoQ) to the MAH in relation to the study results. For further background information, see [PRAC minutes February 2018](#). The MAH replied to the RMS (NL) request for supplementary information, and the responses were assessed by the RMS. The RMS concluded that the MAH has presented sufficient clarification and concluded that the responses given do not indicate that the validity

<sup>60</sup> Update section 4.4 of the SmPC. The package leaflet is updated accordingly

of the results of the INAS study should be questioned. Therefore, the Netherlands considered that the PI changes as proposed by the MAH could be acceptable, provided the further changes recommended by the RMS are implemented. The Netherlands requested PRAC advice on its assessment, conclusions and proposals for PI update.

### Summary of advice

- The PRAC reviewed the assessment, conclusions and recommendations by the RMS (NL), but highlighted a limited study power to show a difference in the VTE risk associated with Qlaira (DNG/EV) in comparison to specific COCs, including levonorgestrel (LNG)-containing COCs, as the study was designed to exclude a 2-fold increase in comparison to all other COCs. Uncertainties in relation to the robustness of the study results were noted which would not enable clear quantification of the VTE risk associated with Qlaira (DNG/EV) in comparison with LNG containing COCs, in line with the approach taken for the PI for all COCs following the referral procedure. As such, any recommendations for PI amendments of Qlaira (DNG/EV) to reflect the VTE risk based on the findings of the INAS-SCORE single study cannot be agreed at this stage. Therefore, and in order to better quantify the VTE risk associated with Qlaira (DNG/EV), the PRAC supported a second request for supplementary information (RSI) to the MAH (in which the MAH would be requested to discuss whether any further data on the VTE risk of Qlaira (DNG/EV) as compared to LNG-containing COCs is available in addition to the INAS-SCORE study, the possibility of inclusion of these further data in a meta-analysis; and the provision of respective analyses with details of the other relevant studies, if applicable).
- Finally, the PRAC advised the RMS to bring back to PRAC, as part of a second follow-up Member State's request for PRAC advice, its updated assessment and conclusions on the MAH's responses to the second RSI, for further Committee advice.

## 11.2. Other requests

### 11.2.1. Flecainide (NAP) - NO/H/PSUFU/00001396/201706

---

Applicant(s): Meda Pharma GmbH & Co. KG, Laboratorios Liconsa S.A., Aurobindo Pharma (Malta) Limited

PRAC Lead: Karen Pernille Harg

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure on antiarrhythmic efficacy of flecainide in combination with beta blockade in patients carrying the Gly389 variant in the beta1 adrenoceptor gene, including a consultation of the CHMP Pharmacogenomics Working Party (PgWP) as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on flecainide (PSUSA/00001396/201706) concluded in March 2018

#### Background

Flecainide is a class 1 anti-arrhythmic (local anaesthetic) agent indicated in the treatment of supraventricular arrhythmia and ventricular arrhythmia.

At its meeting in March 2018, the PRAC considered that the antiarrhythmic efficacy of flecainide in combination with beta blockade in patients carrying the Gly389 variant in the beta-1 adrenoceptor gene needed further assessment. The PRAC also considered it would be

of value to consult the Pharmacogenomics Working Party ([PgWP](#)) and request the MAH(s) to answer a list of questions (LoQ). For further background information, see [PRAC minutes March 2018](#). CMDh further adopted a LoQ for the MAHs. For further background information, see [CMDh minutes March 2018](#).

In the context of the evaluation of the MAHs answers in an informal work-sharing procedure (NO/H/PSUFU/00001396/201706), Norway, the RMS, requested PRAC advice on its assessment.

#### **Summary of advice**

- Based on the review of the available information, the PRAC supported the RMS position that in line with the opinion of the PgWP, no changes to the product information are needed.

### **11.2.2. Fluoxetine (NAP) - FR/H/PSUFU/00001442/201709**

---

Applicant(s): Eli Lilly

PRAC Lead: Ghania Chamouni

Scope: PRAC consultation on a worksharing PSUR follow-up (PSU FU) procedure conducted within the EU network on: 1) MAH's detailed reviews on the risk of autism spectrum disorders (ASD) and on the risk of other neurodevelopmental disorders after in-utero exposure to selective serotonin reuptake inhibitors (SSRI) in general and to fluoxetine in particular; 2) MAH's detailed review on cardiac valve disorders, as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on fluoxetine (PSUSA/00001442/201709) concluded in May 2018

#### **Background**

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depression with or without associated anxiety, for the treatment of obsessive compulsive disorder (OCD) and panic disorder. It is also indicated for the treatment of bulimia nervosa and premenstrual dysphoric disorder (PMDD). Lastly, fluoxetine is indicated in combination with olanzapine for depressive episodes associated with bipolar disorder and treatment of adult patients with treatment-resistant depression.

At its meeting in May 2018, the PRAC considered that the risk of autism spectrum disorders (ASD) and the risk of neurodevelopmental disorder other than ASD, after in utero exposure to SSRI in general and to fluoxetine in particular, as well as the risk of cardiac valve disorders needed further assessment. For further background information, see [PRAC minutes May 2018](#). CMDh further adopted a LoQ for the MAHs. For further background information, see [CMDh minutes May 2018](#).

In the context of the evaluation of the MAHs answers in an informal work-sharing procedure (FR/H/PSUFU/00001442/201709), France, the RMS, requested PRAC advice on its assessment.

#### **Summary of advice**

- Based on the review of the available information, the PRAC supported the RMS position that no changes to the product information (PI) or RMP are warranted at this stage. However, the MAH should continue to monitor cardiac valve disease and neurodevelopmental disorders through routine pharmacovigilance and provide an

analysis of new publications regarding neurodevelopmental disorders following in utero exposure to SSRI in general and to fluoxetine in particular in the next PSUR.

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

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

#### **12.1.1. PRAC Chairperson - election**

---

The mandate of the current PRAC Chairperson, June Raine, will end in September 2018 after serving the maximum of two 3-year mandates. The election for a new Chairperson with a mandate starting in September 2018 took place on 11 July 2018. The EMA Secretariat thanked June Raine for her contribution to the Committee work those past 6 years and reminded the PRAC members of the Rule of Procedure ([EMA/PRAC/567515/2012 Rev.1](#)) pertaining to the election of the Chairperson as well as the election process. Candidate(s) addressed the PRAC. The election took place in the presence of 35 PRAC members out of which 33 were eligible to vote (Iceland and Norway do not vote for the PRAC Chairperson election as per the PRAC Rules of Procedure). Sabine Straus, PRAC member for the Netherlands, was elected as PRAC Chair. Her mandate will start on 3 September 2018 for a term of three years, which may be prolonged once. It will coincide with the first day of the PRAC meeting September 2018. The newly elected Chair thanked June Raine, the PRAC Chair, for her contributions to the PRAC over the last 6 years. June Raine resumed her role as PRAC Chair for the July 2018 meeting. She will remain the PRAC Chair until 2 September 2018 inclusive. Of note, the PRAC vice-Chair election is scheduled in September 2018.

#### **12.1.2. PRAC working group - Best practice guide – recommendations on efficiency of plenary meetings - implementation**

---

PRAC lead: Martin Huber, Ulla Wändel Liminga, Menno van der Elst, Tatiana Magálová, Ghania Chamouni, Albert van der Zeijden, Jan Neuhauser

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#) for revision 1) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#) for revision 1), the PRAC was updated at the organisational matters teleconference held on 26 July 2018 on quantitative measures collected for the PRAC meetings in the second quarter of 2018. See previous update, [PRAC minutes April 2018](#).

### **12.2. Coordination with EMA scientific committees or CMDh-v**

None

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

None

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

### **12.4.1. Reflection paper on the use of extrapolation in the development of medicines for paediatrics**

---

Further to the discussion at the June 2018 PRAC meeting (see [PRAC minutes June 2018](#)), at the organisational matters teleconference held on 26 July 2018, the EMA Secretariat presented to the PRAC for adoption the final version of the reflection paper on the 'use of extrapolation in the development of medicines for paediatrics' following its adoption by the PDCO. Further to the review by the Guideline Consistency Group, it will be adopted by the CHMP in September 2018.

Post-meeting note: On 07/08/2018, the PRAC adopted via written procedure the reflection paper on the 'use of extrapolation in the development of medicines for paediatrics'.

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

None

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

None

## **12.7. PRAC work plan**

### **12.7.1. PRAC work plan 2018 – status update**

---

PRAC lead: June Raine, Almath Spooner

At the organisational matters teleconference held on 26 July 2018, the EMA Secretariat presented to PRAC a mid-year status update on the activities described in the [PRAC work plan 2018](#). The PRAC will now initiate its work plan for 2019 taking into account the activities completed, progress made, priorities identified at the level of the Committee, EMA, HMA and EU network as well as the EMA business continuity plan (BCP) and Brexit preparedness.

## **12.8. Planning and reporting**

### **12.8.1. European Commission (EC) report on performance of pharmacovigilance tasks - second three-yearly report**

---

The PRAC contributed previously to a similar three-yearly report by the European Commission on the performance of pharmacovigilance tasks (2012–2014). For further background, see [PRAC minutes May 2015](#) and [PRAC minutes July 2015](#). The EMA Secretariat reminded the PRAC of the legal framework that foresees a report on the performance of the EU Member States activities relating to the pharmacovigilance (Article 108b of Directive 2001/83/EC and Article 29 of Regulation 726/2004). The anticipated timelines as well as a draft structure of the report covering activities completed between January 2015 and December 2018 were presented. Members States were informed that they might be approached for information on certain activities.

#### 12.8.2. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q2 2018 and predictions

---

At the organisational matters teleconference held on 26 July 2018, the EMA secretariat presented quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators, as well as some predictions in terms of workload by procedure type, where available, and per EU National Competent Authority (NCA) for the upcoming months. For previous update, see [PRAC minutes May 2018](#).

#### 12.8.3. Marketing authorisation applications (MAA) expected for 2018 – planning update dated Q2 2018

---

At the organisational matters teleconference held on 26 July 2018 the EMA Secretariat presented for information an updated report on marketing authorisation applications planned for submission (the business ‘pipeline’). For previous update, see [PRAC minutes January 2018](#).

#### 12.8.4. PRAC workload statistics – Q2 2018

---

At the organisational matters teleconference held on 26 July 2018 the EMA secretariat presented quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. See previous update, [PRAC minutes April 2018](#).

### 12.9. Pharmacovigilance audits and inspections

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

---

None

#### 12.9.2. Pharmacovigilance inspections

---

None

#### 12.9.3. Pharmacovigilance audits

---

None

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

#### 12.10.1. Periodic safety update reports single assessment (PSUSA) –Section on other considerations and follow-up procedures (PSUFU) for nationally approved products (NAPs)

---

PRAC lead: Menno van der Elst

As a follow-up to the previous discussion dated April 2018 (see [PRAC minutes April 2018](#)), the EMA Secretariat gave further guidance to PRAC on the handling of the section on ‘other considerations’ for CMDh as an outcome of a PSUR single assessment procedure. The different scenarios where such a section is to be completed were described. In particular,

the possibility to request a follow-up procedure (PSU FU) for nationally approved products (NAPs) was detailed. However, it was flagged this should remain exceptional and duly justified. The PRAC agreed to monitor the use of the section on 'other considerations' and requested a status update in Q3 2018 – Q1 2019.

#### **12.10.2. Periodic safety update reports**

---

None

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

---

PRAC lead: Menno van der Elst, Maia Uusküla

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

#### **12.10.4. PSURs repository**

---

None

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

---

The PRAC endorsed the draft revised EURD list, version July 2018, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of July 2018, the updated EURD list was adopted by the CHMP and CMDh at their July 2018 meetings and published on the EMA website on 31/07/2018, see:

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

### **12.11. Signal management**

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

---

PRAC lead: Sabine Straus

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) meeting held on 9 July 2018. The SMART WG followed up on the possible challenges for communication at national level in discussing the PRAC recommendation and communication aspects for signals, including 'key messages' for communication at national level. In addition, the SMART WG finalised its discussion on the practical considerations regarding the electronic reaction monitoring report (eRMR) with the agreement on adding a reference to the 'Guidance for signal detection of terms linked to already listed terms in the published User Manual of the electronic Reaction Monitoring Report (eRMR) for National Competent Authorities and EMA'.



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

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

---

None

### **12.12.2. Additional monitoring**

---

None

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

---

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

Post-meeting note: The updated additional monitoring list was published on 25/07/2018 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#)).

## **12.13. EudraVigilance database**

### **12.13.1. Activities related to the confirmation of full functionality**

---

None

### **12.13.2. EudraVigilance (EV) - Clarification for MAHs on recording of individual case safety reports (ICSRs) accessed in EV**

---

Following requests for clarification from MAHs and discussion at the EudraVigilance Expert Group ([EV-EWG](#)), the EMA Secretariat further consulted the European Commission (EC) and the Pharmacovigilance Inspectors Working Group ([PhV IWG](#)) based on the orientation given by PRAC in March 2018 on the most appropriate option. For further background, see [PRAC minutes March 2018](#). The proposed criteria to determine the pharmacovigilance obligations that trigger the processing of individual case safety reports (ICSRs) by a MAH submitted directly by other MAHs through EudraVigilance as developed by the EV-EWG were discussed and endorsed at PRAC.

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

### **12.14.1. Risk management systems**

---

None

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

---

None

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

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

---

None

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

---

None

## **12.16. Community procedures**

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

---

None

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

None

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

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

---

None

### **12.18.2. Safety communication**

---

None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

---

None

## **12.20. Others**

### **12.20.1. Centrally authorised products (CAP) - implementation of electronic signature(s) for divergent position(s) in procedures adopted by majority**

---

The EMA Secretariat presented to PRAC a proposal to extend the electronic process for the endorsement of divergent signatures for procedures involving centrally authorised product(s) across all EMA Committees, i.e. to terminate the need for physical signatures from the divergent position documents. The process is already in place at PRAC for referral procedures following the successful completion in 2017 of a pilot phase (see [PRAC minutes July 2017](#)).

Post-meeting note: On 14/08/2018, the PRAC agreed via written procedure on the replacement of physical signatures for divergent positions with electronic signatures for all procedures.

#### 12.20.2. EMA relocation to Amsterdam, the Netherlands - update

---

As a follow-up to the previous discussion on the EMA relocation in 2019 to Amsterdam, the Netherlands (see [PRAC minutes April 2018](#)), the PRAC was further updated on the status and plans for the relocation. A [tracking tool](#) is available on the EMA website. On 7 June 2018, a new 'Relocate EMA' website was launched by the Dutch government providing information on what has been done so far and what actions will be taken in the coming months. Finally, the meeting schedule for February and March 2019 was presented to the PRAC.

#### 12.20.3. Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population-specific considerations IV: 'Paediatric pharmacovigilance'

---

As a follow-up to the PRAC adoption of the revised draft Guideline on Good Pharmacovigilance Practices (GVP) – Product- or population- specific considerations IV: Paediatric population in May 2018 (see [PRAC minutes May 2018](#)), the EMA Secretariat informed the PRAC that following adoption by the other EMA Committees and legal and quality review, and in absence of changes, the document is considered final and will be published on the EMA website.

#### 12.20.4. Medical device and in vitro diagnostic regulation - EMA implementation plan for the new legislation

---

The EMA Secretariat presented to PRAC the EMA implementation plan for the new regulations for medical devices (Medical Devices Regulation (EU) 2017/745) and in vitro diagnostics (In Vitro Diagnostic Regulation (EU) 2017/746) highlighting the important changes introduced by the new regulations and focussing on the impact for EMA/EU NCAs. Of note, EMA will be informed in the case of a serious incident or field safety corrective action in relation to companion diagnostics as per Article 84 (6) of 2017/746 as well as to medical devices with an ancillary medicinal substance if related to the substance as per Article 89(6) of 2017/745. The medical device regulation has a 3-year transition period (26 May 2020) and the in vitro diagnostic regulation, a 5-year transition period (26 May 2022).

#### 12.20.5. Strategy on measuring the impact of pharmacovigilance - update on prioritised impact research topics

---

Further to the prioritisation of impact research topics by the PRAC interest group (IG) Impact the EMA Secretariat presented together with the Chair of the IG Impact a list of topics for independent impact research, together with study objectives for further prioritisation and PRAC endorsement. The PRAC endorsed two impact research topics on valproate and retinoids respectively. PRAC delegates were requested to review the full list of impact research topics and were invited to propose concrete study objectives and endpoints for their prioritised topic(s). Answers should be sent by 31 August 2018. Further discussion is scheduled in September 2018.

Post-meeting note: On 27/07/2018, the PRAC adopted the PRAC IG's proposal amending selected post-authorisation assessment report (AR) templates with a new section on 'impact research', replacing the monthly notification process of PRAC Rapporteurs to identify and prioritise topics for impact research.

## 13. Any other business

At the organisational matters teleconference held on 26 July 2018, the Netherlands shared new safety information on the premature termination of a clinical trial with sildenafil (Dutch STRIDER trial) conducted in the Netherlands by a non-commercial sponsor. (See 4.2.4. ).

Next meeting on: 03-06 September 2018

## 14. Annex I – Signals assessment and prioritisation<sup>61</sup>

### 14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables<sup>62</sup>.

#### 14.1.1. Dasabuvir – EXVIERA (CAP); ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP)

Applicant(s): AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Signal of interstitial lung disease

EPITT 19257 – New signal

Lead Member State(s): ES

#### 14.1.2. Montelukast (NAP)

Applicant(s): various

PRAC Rapporteur: Kimmo Jaakkola

Scope: Signal of dysphemia (speech disorders)

EPITT 19275 – New signal

Lead Member State(s): FI

#### 14.1.3. Pembrolizumab – KEYTRUDA (CAP)

Applicant(s): Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Signal of systemic inflammatory response syndrome (SIRS)

<sup>61</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

<sup>62</sup> Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

EPITT 19267 – New signal

Lead Member State(s): NL

#### 14.1.4. Perindopril (NAP)

---

Applicant(s): various

PRAC Rapporteur: Doris Stenver

Scope: Signal of Raynaud's phenomenon

EPITT 19248 – New signal

Lead Member State(s): DK

### 14.2. New signals detected from other sources

#### 14.2.1. Olmesartan (NAP)

---

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of risk of autoimmune hepatitis

EPITT 19258 – New signal

Lead Member State(s): DE, NL

#### 14.2.2. Ranibizumab – LUCENTIS (CAP)

---

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of angioedema

EPITT 19245 – New signal

Lead Member State(s): SE

#### 14.2.3. Thiamazole (NAP)

---

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Signal of pancreatitis

EPITT 19274 – New signal

Lead Member State(s): DE

#### 14.2.4. Vemurafenib – ZELBORAF (CAP)

---

Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of cardiac failure

## **15. Annex I – Risk management plans**

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

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

#### **15.1.1. Axalimogene filolisbac - EMEA/H/C/004473**

ATMP<sup>63</sup>

Scope: Treatment of cervical cancer

#### **15.1.2. Doxorubicin hydrochloride - EMEA/H/C/004110**

Scope: Treatment of breast and ovarian cancer

#### **15.1.3. Pegfilgrastim - EMEA/H/C/004802**

Scope: Treatment of neutropenia

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

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

#### **15.2.1. Bosentan - STAYVEER (CAP) - EMEA/H/C/002644/II/0023**

Applicant: Marklas Nederlands BV

PRAC Rapporteur: Caroline Laborde

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional post-approval safety study and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

#### **15.2.2. Bosentan - TRACLEER (CAP) - EMEA/H/C/000401/II/0086**

Applicant: Actelion Registration Limited

PRAC Rapporteur: Caroline Laborde

---

<sup>63</sup> Advanced therapy medicinal product

Scope: Update of Annex II.D following the submission of the thirteenth and final study report for the DUO registry (listed as a category 3 study in the RMP): a non-interventional PASS and additional risk minimisation measure in the bosentan EU RMP. The RMP (version 9.1) is updated accordingly

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

---

Applicant: Pfizer Limited

PRAC Rapporteur: Martin Huber

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

#### 15.2.4. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/II/0060

---

Applicant: Hospira UK Limited

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

#### 15.2.5. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/II/0051

---

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 8.0) to introduce the new RMP template, update some milestones of the pharmacovigilance plan and delete some safety concerns from the educational material to healthcare professionals

#### 15.2.6. Meningococcal group A, C, W135 and Y conjugate vaccine - NIMENRIX (CAP) - EMEA/H/C/002226/II/0078

---

Applicant: Pfizer Limited

PRAC Rapporteur: Julie Williams

Scope: Update of the RMP (version 8.0) to reflect changes requested in the conclusions of variations II/49 and II/73 adopted by CHMP in November 2016 and February 2018 respectively. The RMP is also revised to get aligned with the current EU RMP template, as per GVP module V revision 2 on 'Risk management systems' including proposals for the removal of some important potential risks: 'Guillain-Barré syndrome', 'purpura', 'vasculitis', 'acute disseminated encephalomyelitis', 'brachial neuritis', 'anaphylaxis', 'change in meningococcal epidemiology/serogroup replacement', 'lack of efficacy', 'administration via the intravascular', 'intradermal or subcutaneous route', and 'administration to patients with

thrombocytopenia or any coagulation disorder with a risk of haemorrhage'. In addition, the MAH proposed to remove the missing information on 'use in patients with chronic diseases' and 'use during pregnancy and lactation'

#### 15.2.7. [Nilotinib - TASIGNA \(CAP\) - EMEA/H/C/000798/II/0092, Orphan](#)

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 21.0) in order to delete 'myelosuppression' as an important identified risk and to reclassify 'cardiac failure' from an important potential to an important identified risk. In addition, changes in the definition of the identified risks 'hepatotoxicity' and 'fluid retention' have been implemented

#### 15.2.8. [Osimertinib - TAGRISSO \(CAP\) - EMEA/H/C/004124/II/0023](#)

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Sabine Straus

Scope: Update of the RMP (version 9) in order to remove PASS D5160C00022 (listed as a category 3 study in the RMP): 'an open label, multinational, multicentre, real world treatment study of single agent osimertinib for patients with advanced/metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI) (ASTRIS)' from the pharmacovigilance plan

#### 15.2.9. [Pegfilgrastim - NEULASTA \(CAP\) - EMEA/H/C/000420/II/0099](#)

---

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Update of the RMP (version 5.1) in order to add study 20160176 (listed as category 3 in the RMP): a retrospective cohort study of female breast cancer patients aged 66 years and over selected from the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to estimate the risk of acute myeloid leukaemia/myelodysplastic syndrome for breast cancer patients, as a new pharmacovigilance activity. In addition, the MAH submitted a draft protocol for study 20160176

#### 15.2.10. [Rituximab - MABTHERA \(CAP\) - EMEA/H/C/000165/II/0144](#)

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 16.0) to remove the additional risk minimisation measure of educational outreaches for the important identified risk of 'infusion related reactions' and 'acute infusion related reactions' (IRR)



**15.2.11. Zoledronic acid - ZOLEDRONIC ACID MYLAN (CAP) - EMEA/H/C/002482/WS1370/0015**

---

Applicant: Mylan S.A.S

PRAC Rapporteur: Doris Stenver

Scope: Update of the RMP (version 7.0) to implement the latest RMP template and to include 'and other anatomical sites' in addition to 'osteonecrosis of the jaw' as an important identified risk, to be aligned with the conclusions of the PSUSA procedure for zoledronic acid (PSUSA/00003149/201608) concluded by PRAC/CHMP in April 2017

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

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

**15.3.1. Abatacept - ORENCIA (CAP) - EMEA/H/C/000701/X/0117/G**

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped applications consisting of: 1) extension application to add two new strengths of 50 mg and 87.5 mg for solution for injection in a pre-filled syringe with needle guard for subcutaneous (SC) administration; 2) variation to include paediatric use of polyarticular juvenile idiopathic arthritis (2 years and above) for solution for injection (50 mg, 87.5 mg and 125 mg). The RMP (version 25.0) is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the product information

**15.3.2. Blinatumomab - BLINCYTO (CAP) - EMEA/H/C/003731/II/0011, Orphan**

---

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Eva Jirsová

Scope: Extension of indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and amend the safety information. The labelling and the RMP (version 4.0) are updated accordingly

**15.3.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/II/0034**

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from the CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel,

placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly

#### 15.3.4. [Canagliflozin, metformin - VOKANAMET \(CAP\) - EMEA/H/C/002656/II/0034](#)

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC in order to include the safety and efficacy information on cardiovascular events following the final results from CANVAS programme consisting of study DIA3008 (CANVAS study): a phase 3 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM); and study DIA4004 (CANVAS-R study): a phase 4 randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM. The package leaflet and the RMP (version 7.2) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to bring the product information in line with the latest QRD template (version 10)

#### 15.3.5. [Daratumumab - DARZALEX \(CAP\) - EMEA/H/C/004077/II/0011, Orphan](#)

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Extension of indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 3.1) are updated accordingly. In addition, the MAH took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the package leaflet

#### 15.3.6. [Decitabine - DACOGEN \(CAP\) - EMEA/H/C/002221/II/0033, Orphan](#)

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ghania Chamouni

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

#### 15.3.7. Dupilumab - DUPIXENT (CAP) - EMEA/H/C/004390/X/0004/G

---

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP); 2) extensions of indication to add as indications: 'add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype', 'maintenance therapy to improve lung function' and 'maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients' based on pivotal studies, namely: study DRI12544: a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma; study LIBERTY ASTHMA QUEST: a randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma; and study VENTURE: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 are updated. The package leaflet and the RMP (version 2.0) are updated accordingly. In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths

#### 15.3.8. Eltrombopag - REVOLADE (CAP) - EMEA/H/C/001110/II/0049

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include first line treatment of adult and paediatric patients aged 2 years and older with severe aplastic anaemia. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 50.0) are updated accordingly

#### 15.3.9. Eluxadoline - TRUBERZI (CAP) - EMEA/H/C/004098/II/0005/G

---

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Grouped variations consisting of: 1) submission of the final report from study ELX-PH-08 (listed as a category 3 study in the RMP). This is an in vitro evaluation study aimed to investigate the effects on treating primary cultures of cryopreserved human hepatocytes with eluxadoline on the expression of cytochrome P450 (CYP) enzymes; 2) submission of the final report from study 3030-102-002 (listed as a category 3 study in the RMP). This is a randomised, open label study aimed to evaluate the effect of eluxadoline as a potential time dependent inhibitor of CYP3A4<sup>64</sup> with the substrate midazolam. The RMP (version 2.0) is updated to refine the important identified risk of 'sphincter of Oddi (SO) spasm' to 'SO spasm (sphincter of Oddi dysfunction, SOD)' and to include pancreatitis as an important

---

<sup>64</sup> Cytochrome P 450 3A4

identified risk as agreed in the conclusions of PSUSA/00010528/201703 finalised at PRAC/CHMP in October 2017

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

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII (FVIII) inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the following pivotal trials: 1) study BH30071 (HAVEN 3): an ongoing, multicentre, open-label, randomized phase 3 clinical study evaluating the efficacy, safety and pharmacokinetic (PK) of emicizumab prophylaxis at doses of 1.5 mg/kg/week (QW) and 3 mg/kg/every 2 weeks (Q2W) versus no prophylaxis in adults and adolescent patients (age of 12 or above) with haemophilia A without inhibitors against FVIII; 2) study BO39182 (HAVEN 4): an ongoing multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab given as the dose of 6 mg/kg/every 4 weeks (Q4W) in adults and adolescent patients (age of 12 or above) with haemophilia A with or without FVIII inhibitors; 3) study BH29992 (HAVEN 2): a multicentre, open-label, non-randomized phase 3 study evaluating the efficacy, safety and PK of emicizumab at the QW dose in paediatric patients (<12 years old or 12-17 years old and <40kg) with haemophilia A with FVIII inhibitors. The package leaflet and the RMP (version.2.0) are updated accordingly. In addition, the MAH took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC

#### 15.3.11. Enzalutamide - XTANDI (CAP) - EMEA/H/C/002639/II/0039/G

---

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC). As a consequence, sections 4.1 and 5.1 of the SmPC are updated based on the supportive clinical study results of study MDV3100-14 (PROSPER): a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer; study MDV3100-09 (STRIVE): a multicentre phase 2 study to investigate the safety and efficacy of enzalutamide versus bicalutamide in men with non-metastatic or metastatic castration-resistant prostate cancer; and based on supportive non-clinical data from 7 new reports. The package leaflet and the RMP (version 12.1) are updated accordingly; 2) update of sections 4.4, 4.7, 4.8 and 5.2 of the SmPC in order to amend the warning on possible association with seizure, the effects on driving or operating machines, the identified adverse reactions and to amend the 'race' subsection regarding pharmacokinetic properties based on the results from the completed study PROSPER (a phase 3 randomized controlled study, designed to investigate the safety and efficacy of enzalutamide in patients with non-metastatic castration-resistant prostate cancer) and study Asian PREVAIL (a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral enzalutamide in chemotherapy-naïve subjects with progressive metastatic prostate cancer who have failed androgen deprivation therapy); as well as the updated integrated clinical safety database. The package leaflet is updated

accordingly

**15.3.12. Epoetin alfa - ABSEAMED (CAP) - EMEA/H/C/000727/WS1406/0070; BINOCRIT (CAP) - EMEA/H/C/000725/WS1406/0070; EPOETIN ALFA HEXAL (CAP) - EMEA/H/C/000726/WS1406/0069**

---

Applicant: Sandoz GmbH

PRAC Rapporteur: Ghania Chamouni

Scope: Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of  $\leq 10$  g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin ( $< 200$  mU/ml). As a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The package leaflet and the RMP (version 17.0) are updated accordingly. In addition, the MAH took the opportunity to align information with the reference medicinal product and with the EC guideline on excipients to improve the quality and readability of the translations in the product information and to update Annex A in line with the relevant EMA guideline

**15.3.13. Erlotinib - TARCEVA (CAP) - EMEA/H/C/000618/II/0058**

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Update of sections 4.2, and 5.1 of the SmPC based on phase 3 clinical study MO22162 (CURRENTS) comparing a higher dose of Tarceva (300 mg) over the recommended daily dose (150 mg) in current smokers with locally advanced or metastatic non-small cell lung cancer (NSCLC) in the second-line setting after failure of chemotherapy. The package leaflet and the RMP (version 7.0) are updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in sections 4.4, 4.5, 4.6, 4.7, 4.8 and 5.2 of the SmPC

**15.3.14. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/X/0044/G**

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Grouped application consisting of: 1) extension application to introduce a new strength of hard capsules (0.25 mg) to the currently approved presentations; 2) extension of indication to add a new indication for the treatment of paediatric patients of 10 years of age and above with relapsing multiple sclerosis (RMS). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3, 6 and 8 of the SmPC are updated. The package leaflet, labelling and the RMP (version 13.0) are updated accordingly. In addition, Annex II is updated to be brought in line with the latest QRD template (version 10)

**15.3.15. Guselkumab - TREMFYA (CAP) - EMEA/H/C/004271/II/0002/G**

---

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of sections 1, 2, 3, 5.1, 6.4, 6.5, 6.6, of the SmPC based on the results from study CNTO1959PSO3006: an open-label, randomized study to assess the design features of an investigational prefilled syringe-facilitated injection device (PFS-FID) and the ability of subjects with rheumatoid arthritis or psoriasis to self-administer placebo with the PFS-FID. In addition, the MAH included a new presentation, constituting a pre-filled syringe assembled with a patient facilitated, manually operated pre-filled pen, referred to as 'SelfDose'. The package leaflet, labelling and the RMP (version 2.0) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

#### 15.3.16. [Human coagulation factor X - COAGADEX \(CAP\) - EMEA/H/C/003855/II/0007, Orphan](#)

---

Applicant: Bio Products Laboratory Limited

PRAC Rapporteur: Julie Williams

Scope: Update of section sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include safety and efficacy data in children aged less than 12 years of age based on final results from study Ten02: a phase 3 open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of Bio Products Laboratory (BPL)'s high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years, provided in accordance with the agreed paediatric investigational plan (PIP). The package leaflet and the RMP (version 7.0) are updated accordingly

#### 15.3.17. [Infliximab - REMICADE \(CAP\) - EMEA/H/C/000240/II/0209](#)

---

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.4 of the SmPC to amend the current warning on colon cancer and dysplasia based on the final report of the OPUS registry (P04808): a prospective, observational, non-interventional, post-marketing safety surveillance programme in subjects with ulcerative colitis (UC). The provision of the study report fulfils MEA 121. In addition, the MAH took the opportunity to add a warning on screening tests for tuberculosis to align it with current medical practice, to add a reminder on the patient alert card in the package leaflet. Furthermore, the MAH introduced some editorial changes in line with the latest QRD template. The RMP (version 14.1) is updated accordingly

#### 15.3.18. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1278/0042; Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1278/0053](#)

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of Opdivo and Yervoy SmPCs are updated. The package leaflet and the RMP (version 19.0 for Yervoy and version 13.0 for Opdivo) are updated accordingly. In addition, the MAH took the opportunity to correct some typos throughout the Yervoy (ipilimumab) and Opdivo (nivolumab) product information

15.3.19. [Nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1372/0053](#);  
[Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1372/0057](#)

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information from pivotal study CA209227: an open-label, randomised phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent NSCLC. The package leaflet and RMP (version 14.0 for Opdivo and version 21.0 for Yervoy) are updated accordingly. In addition, the MAH has taken the opportunity to introduce minor editorial and formatting revisions in the product information

15.3.20. [Lenvatinib - KISPLYX \(CAP\) - EMEA/H/C/004224/WS1396/0011](#); [LENVIMA \(CAP\) - EMEA/H/C/003727/WS1396/0015](#)

---

Applicant: Eisai Europe Ltd.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of section 4.5 of the SmPC to include that there is no significant drug-drug interaction (DDI) risk with midazolam based on the results of study E7080-A001-109: a phase 1 study to determine DDI of lenvatinib and midazolam, a cytochrome P450 3A4 (CYP3A4) substrate, in subjects with advanced solid tumours. The RMP (version 10.4) is updated accordingly

15.3.21. [Mepolizumab - NUCALA \(CAP\) - EMEA/H/C/003860/II/0013/G](#)

---

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of extension of indication to include children and adolescents aged 6 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC and sections 1, 2, 3, 4 and information for healthcare professionals in the package leaflet are updated accordingly. In addition to the proposed SmPC/package leaflet updates specific to the paediatric indication, the MAH proposed to include some wording to ensure the name and batch number of the administered product should be clearly recorded in the patient file. The RMP (version 3) is updated accordingly; as well as quality variations

15.3.22. [Ocrelizumab - OCREVUS \(CAP\) - EMEA/H/C/004043/II/0002](#)

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4 and 4.5 of the SmPC in order to include information on vaccination based on interim results from study BN29739 (listed as a category 3 study in the RMP): a phase 3b, multicentre, randomised, parallel-group, open-label study to evaluate the effects of ocrelizumab on immune response in patients with relapsing forms of



multiple sclerosis (MS). The package leaflet and the RMP (version 2.0) are updated accordingly

#### 15.3.23. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0047

---

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Sabine Straus

Scope: Extension of indication to include (as monotherapy) adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection, based on study KEYNOTE-054: a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (stages IIIA [ $> 1$  mm lymph node metastasis], IIIB and IIIC). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 17.1) are updated accordingly

#### 15.3.24. Rituximab - RIXATHON (CAP) - EMEA/H/C/003903/WS1335/0010; RIXIMYO (CAP) - EMEA/H/C/004729/WS1335/0010

---

Applicant: Sandoz GmbH

PRAC Rapporteur: Doris Stenver

Scope: Submission of the final clinical study reports (CSR) for: 1) study GP13-302: a randomized, double-blind, parallel-group safety study with the aim to specifically address a potential safety risk of a switch from treatment with originator rituximab containing product to treatment with GP2013 (biosimilar rituximab containing products); 2) study GP13-201: a 52-week multicentre, randomized, double-blind, parallel-arm, comparative study in patients with active rheumatoid arthritis (RA) refractory or intolerant to standard disease modifying anti-rheumatic drugs (DMARDs) and one or up to three anti-tumour necrosis factor (TNF) therapies. The RMP (version 3.0) is updated accordingly

#### 15.3.25. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/II/0058

---

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for Xarelto 2.5 mg co-administered with acetylsalicylic acid. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The package leaflet, labelling and the RMP (version 11.1) are updated accordingly. In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data

#### 15.3.26. Rolapitant - VARUBY (CAP) - EMEA/H/C/004196/II/0007/G

---

Applicant: Tesaro UK Limited

PRAC Rapporteur: Adam Przybylkowski



Scope: Grouped variations consisting of: 1) update of SmPC section 4.5 regarding interaction with organic cation transporter 1 (OCT1) substrates to reflect results from non-clinical study 17TESAP2R1: an in vitro evaluation of the substrate and inhibitor potential of rolapitant for efflux and update of transporters; 2) update of SmPC section 4.5 regarding interaction with UDP-glucuronosyltransferase (UGT) substrates following the submission of the results from non-clinical studies, namely: study 170594: evaluation of potential UGT inhibition by rolapitant in cryopreserved human hepatocytes and study TSRP/REP/07CRD75486/2017: evaluation of potential rolapitant metabolism by recombinantly expressed human UGT enzymes; 3) update of SmPC section 4.5 following the submission of the results for study 1000-01-001: an open-label, single-dose study to assess the effects of rolapitant (oral) on the pharmacokinetics of caffeine (CYP1A2) in healthy subjects. The RMP (version 1.2) is updated accordingly

---

**15.3.27. Sevelamer carbonate - RENVELA (CAP) - EMEA/H/C/000993/X/0039**

---

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

---

**15.3.28. Sevelamer carbonate - SEVELAMER CARBONATE ZENTIVA (CAP) - EMEA/H/C/003971/X/0011**

---

Applicant: Genzyme Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Extension application to add a new strength of 0.8 g powder for oral suspension. The RMP (version 9.0) is updated accordingly

---

**15.3.29. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/X/0012**

---

Applicant: Pfizer Limited

PRAC Rapporteur: Sabine Straus

Scope: Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. The extension of indication includes a change in pharmacokinetics. The RMP (version 4.0) is updated accordingly

---

**15.3.30. Trastuzumab - HERZUMA (CAP) - EMEA/H/C/002575/II/0006**

---

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Addition of a new presentation (420 mg/vial) drug product for single-dose, partial use. The strength (concentration after reconstitution) is identical to the previously authorised 150mg/vial presentation. The RMP (version 3.1) is updated accordingly

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of SmPC section 4.4 and 4.8 in order to amend the special warnings and precautions for use on the effects of post-natal development as well as to include a new adverse event (precocious puberty) observed in children in post marketing; 2) submission of the final study report for study ML28296 (post approval commitment MEA 18): a prospective observational study of treatment patterns and effectiveness and safety outcomes in advanced basal cell carcinoma and basal cell carcinoma nevus syndrome patients. The RMP (version 13.0) is updated accordingly. In addition, the MAH took the opportunity to include some editorial changes in the product information

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

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

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

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

#### 16.1.1. Adalimumab<sup>65</sup> - AMGEVITA (CAP), CYLTEZO (CAP), IMRALDI (CAP), SOLYMBIC (CAP) - PSUSA/00010589/201712

---

Applicants: Amgen Europe B.V. (Amgevita, Solymbic), Boehringer Ingelheim International GmbH (Cyltezo), Samsung Bioepis UK Limited (SBUK) (Imraldi)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Afamelanotide - SCENESSE (CAP) - PSUSA/00010314/201712

---

Applicant: Clinuvel (UK) Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

---

<sup>65</sup> Biosimilar products only

#### 16.1.3. Alectinib - ALECENSA (CAP) - PSUSA/00010581/201801

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Amifampridine - FIRDAPSE (CAP) - PSUSA/00000141/201712

---

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Asfotase alfa - STRENSIQ (CAP) - PSUSA/00010421/201801

---

Applicant: Alexion Europe SAS

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Asparaginase alfa - SPECTRILA (CAP) - PSUSA/00010455/201801

---

Applicant: Medac Gesellschaft für klinische Spezialpräparate mbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Beclometasone, formoterol, glycopyrronium bromide - TRIMBOW (CAP) - PSUSA/00010617/201801

---

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Birch bark extract<sup>66</sup> - EPISALVAN (CAP) - PSUSA/00010446/201801

---

Applicant: Amryt AG

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Brodalumab - KYNTHEUM (CAP) - PSUSA/00010616/201801

---

Applicant: LEO Pharma A/S

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

---

<sup>66</sup> Centrally authorised product(s) only

#### 16.1.10. Cenegermin - OXERVATE (CAP) - PSUSA/00010624/201801

---

Applicant: Dompe farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.11. Clofarabine - EVOLTRA (CAP) - PSUSA/00000805/201712

---

Applicant: Genzyme Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

#### 16.1.12. Darunavir - PREZISTA (CAP) - PSUSA/00000934/201712

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.13. Dimethyl fumarate<sup>67</sup> - SKILARENCE (CAP) - PSUSA/00010647/201712

---

Applicant: Almirall S.A

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Edotreotide - SOMAKIT TOC (CAP) - PSUSA/00010552/201712

---

Applicant: Advanced Accelerator Applications

PRAC Rapporteur: Almath Spooner

Scope: Evaluation of a PSUSA procedure

#### 16.1.15. Elbasvir, grazoprevir - ZEPATIER (CAP) - PSUSA/00010519/201801

---

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.16. Epoetin zeta - RETACRIT (CAP), SILAPO (CAP) - PSUSA/00001241/201712

---

Applicant: Hospira UK Limited (Retacrit), Stada Arzneimittel AG (Silapo)

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

---

<sup>67</sup> Indicated in the treatment of psoriasis

**16.1.17. Eptacog alfa - NOVOSEVEN (CAP) - PSUSA/00001245/201712**

---

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Sabine Straus

Scope: Evaluation of a PSUSA procedure

**16.1.18. Human fibrinogen, human thrombin - EVICEL (CAP), RAPLIXA<sup>68</sup>, TACHOSIL (CAP), VERASEAL (CAP) - PSUSA/00010297/201712**

---

Applicants: Omrix Biopharmaceuticals N. V. (Evicel), Mallinckrodt Pharmaceuticals Ireland Limited (Raplixa), Takeda Austria GmbH (TachoSil), Instituto Grifols, S.A. (VeraSeal)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.19. Human papillomavirus 9-valent vaccine (recombinant, adsorbed) - GARDASIL 9 (CAP) - PSUSA/00010389/201712**

---

Applicant: MSD Vaccins

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**16.1.20. Inotuzumab ozogamicin - BESPONSA (CAP) - PSUSA/00010659/201712**

---

Applicant: Pfizer Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.21. Lenalidomide - REVLIMID (CAP) - PSUSA/00001838/201712**

---

Applicant: Celgene Europe BV

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

**16.1.22. Lesinurad - ZURAMPIC (CAP) - PSUSA/00010470/201712**

---

Applicant: Grunenthal GmbH

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

**16.1.23. Liraglutide - SAXENDA (CAP), VICTOZA (CAP) - PSUSA/00001892/201712**

---

Applicant: Novo Nordisk A/S

---

<sup>68</sup> European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Raplixa dated 27 March 2018

PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure

---

16.1.24. [Lutetium \(<sup>177</sup>Lu\) oxodotreotide - LUTATHERA \(CAP\) - PSUSA/00010643/201712](#)

---

Applicant: Advanced Accelerator Applications  
PRAC Rapporteur: Adam Przybylkowski  
Scope: Evaluation of a PSUSA procedure

---

16.1.25. [Matrix-applied characterised autologous cultured chondrocytes - MACI<sup>69</sup> - PSUSA/00010116/201712](#)

---

Applicant: Vericel Denmark ApS, ATMP<sup>70</sup>  
PRAC Rapporteur: Julie Williams  
Scope: Evaluation of a PSUSA procedure

---

16.1.26. [Nonacog gamma - RIXUBIS \(CAP\) - PSUSA/00010320/201712](#)

---

Applicant: Baxalta Innovations GmbH  
PRAC Rapporteur: Brigitte Keller-Stanislowski  
Scope: Evaluation of a PSUSA procedure

---

16.1.27. [Obeticholic acid - OCALIVA \(CAP\) - PSUSA/00010555/201712](#)

---

Applicant: Intercept Pharma Ltd  
PRAC Rapporteur: Menno van der Elst  
Scope: Evaluation of a PSUSA procedure

---

16.1.28. [Olaparib - LYNPARZA \(CAP\) - PSUSA/00010322/201712](#)

---

Applicant: AstraZeneca AB  
PRAC Rapporteur: Amelia Cupelli  
Scope: Evaluation of a PSUSA procedure

---

16.1.29. [Opicapone - ONGENTYS \(CAP\) - PSUSA/00010516/201712](#)

---

Applicant: Bial - Portela & C<sup>a</sup>, S.A.  
PRAC Rapporteur: Dolores Montero Corominas  
Scope: Evaluation of a PSUSA procedure

---

<sup>69</sup> European Commission (EC) decision on the marketing authorisation (MA) withdrawal of Maci dated 1 July 2018

<sup>70</sup> Advanced therapy medicinal product

**16.1.30. Pegaspargase<sup>71</sup> - ONCASPAR (CAP) - PSUSA/00010457/201801**

---

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

**16.1.31. Reteplase - RAPILYSIN (CAP) - PSUSA/00002623/201711**

---

Applicant: Actavis Group PTC ehf

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

**16.1.32. Roflumilast - DAXAS (CAP) - PSUSA/00002658/201801**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

**16.1.33. Sarilumab - KEVZARA (CAP) - PSUSA/00010609/201712**

---

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

**16.1.34. Saxagliptin, dapagliflozin - QTERN (CAP) - PSUSA/00010520/201801**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**16.1.35. Selexipag - UPTRAVI (CAP) - PSUSA/00010503/201712**

---

Applicant: Actelion Registration Limited

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

**16.1.36. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - PSUSA/00010524/201712**

---

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

---

<sup>71</sup> Centrally authorised product(s) only

**16.1.37. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - PSUSA/00010619/201801**

---

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

**16.1.38. Sonidegib - ODOMZO (CAP) - PSUSA/00010408/201712**

---

Applicant: Sun Pharmaceutical Industries Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Evaluation of a PSUSA procedure

**16.1.39. Spheroids of human autologous matrix-associated chondrocytes - SPHEROX (CAP) - PSUSA/00010630/201801**

---

Applicant: CO.DON AG, ATMP<sup>72</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

**16.1.40. Tasimelteon - HETLIOZ (CAP) - PSUSA/00010394/201801**

---

Applicant: Vanda Pharmaceuticals Ltd.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

**16.1.41. Umeclidinium bromide, vilanterol - ANORO (CAP), LAVENTAIR (CAP) - PSUSA/00010264/201712**

---

Applicant: Glaxo Group Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

**16.1.42. Riluzole - RILUTEK (CAP), RILUZOLE ZENTIVA (CAP); NAP - PSUSA/00002645/201712**

---

Applicants: Aventis Pharma S.A. (Rilutek), Zentiva, k.s. (Riluzole Zentiva), various

PRAC Rapporteur: Julie Williams

Scope: Evaluation of a PSUSA procedure

---

<sup>72</sup> Advanced therapy medicinal product



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

### **16.2.1. Human hepatitis B immunoglobulin - ZUTECTRA (CAP); NAP - PSUSA/00001631/201711**

---

Applicants: Biotest Pharma GmbH (Zutectra), various

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

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

### **16.3.1. Alfuzosin (NAP) - PSUSA/00000084/201711**

---

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **16.3.2. Amino acid combinations, glucose, triglyceride combinations<sup>73</sup>, with or without electrolytes, mineral compounds<sup>74 75</sup> (NAP) - PSUSA/00010190/201712**

---

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **16.3.3. Amlodipine, indapamide (NAP); amlodipine, indapamide, perindopril (NAP) - PSUSA/00010358/201711**

---

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

### **16.3.4. Antithrombin III (NAP) - PSUSA/00003159/201712**

---

Applicant(s): various

PRAC Lead: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

### **16.3.5. Bambuterol (NAP) - PSUSA/00000295/201712**

---

Applicant(s): various

---

<sup>73</sup> E.g. olive oil, soya bean oil, fish oil

<sup>74</sup> Intravenous (I.V.) application only

<sup>75</sup> Nationally authorised product Numeta only

PRAC Lead: Ulla Wändel Liminga  
Scope: Evaluation of a PSUSA procedure

---

16.3.6. Bromperidol (NAP) - PSUSA/00000439/201711

---

Applicant(s): various  
PRAC Lead: Sabine Straus  
Scope: Evaluation of a PSUSA procedure

---

16.3.7. Caffeine, drotaverine hydrochloride, metamizol sodium (NAP) - PSUSA/00001996/201711

---

Applicant(s): various  
PRAC Lead: Tatiana Magalova  
Scope: Evaluation of a PSUSA procedure

---

16.3.8. Cetirizine (NAP) - PSUSA/00000628/201711

---

Applicant(s): various  
PRAC Lead: Kirsti Villikka  
Scope: Evaluation of a PSUSA procedure

---

16.3.9. Ciprofloxacin hydrochloride, hydrocortisone (NAP) - PSUSA/00000774/201711

---

Applicant(s): various  
PRAC Lead: Amelia Cupelli  
Scope: Evaluation of a PSUSA procedure

---

16.3.10. Clevidipine (NAP) - PSUSA/00010288/201711

---

Applicant(s): various  
PRAC Lead: Julie Williams  
Scope: Evaluation of a PSUSA procedure

---

16.3.11. Diacerein (NAP) - PSUSA/00001026/201712

---

Applicant(s): various  
PRAC Lead: Caroline Laborde  
Scope: Evaluation of a PSUSA procedure

---

16.3.12. Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated), haemophilus type b conjugate vaccine (adsorbed) (NAP) - PSUSA/00001124/201711

---

Applicant(s): various

PRAC Lead: Brigitte Keller-Stanislowski  
Scope: Evaluation of a PSUSA procedure

---

16.3.13. [Dutasteride \(NAP\); dutasteride, tamsulosine \(NAP\) - PSUSA/00010506/201711](#)

---

Applicant(s): various  
PRAC Lead: Julia Pallos  
Scope: Evaluation of a PSUSA procedure

---

16.3.14. [Econazole \(NAP\); econazole nitrate, triamcinolone acetonide \(NAP\); econazole nitrate, zinc oxide \(NAP\) - PSUSA/00001195/201711](#)

---

Applicant(s): various  
PRAC Lead: Julia Pallos  
Scope: Evaluation of a PSUSA procedure

---

16.3.15. [Fludeoxyglucose \(<sup>18</sup>F\) \(NAP\) - PSUSA/00001437/201711](#)

---

Applicant(s): various  
PRAC Lead: Ghania Chamouni  
Scope: Evaluation of a PSUSA procedure

---

16.3.16. [Glatiramer \(NAP\) - PSUSA/00001529/201711](#)

---

Applicant(s): various  
PRAC Lead: Julie Williams  
Scope: Evaluation of a PSUSA procedure

---

16.3.17. [Levocabastine \(NAP\) - PSUSA/00001849/201711](#)

---

Applicant(s): various  
PRAC Lead: Doris Stenver  
Scope: Evaluation of a PSUSA procedure

---

16.3.18. [Methylprednisolone \(NAP\) - PSUSA/00002026/201711](#)

---

Applicant(s): various  
PRAC Lead: Jan Neuhauser  
Scope: Evaluation of a PSUSA procedure

---

16.3.19. [Rupatadine \(NAP\) - PSUSA/00002673/201712](#)

---

Applicant(s): various  
PRAC Lead: Dolores Montero Corominas

Scope: Evaluation of a PSUSA procedure

#### 16.3.20. Tafluprost, timolol (NAP) - PSUSA/00010324/201712

---

Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

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

#### 16.4.1. Oxybutynin - KENTERA (CAP) - EMEA/H/C/000532/LEG 022

---

Applicant: Nicobrand Limited

PRAC Rapporteur: Laurence de Fays

Scope: Critical assessment as requested in the conclusions of PSUSA/00002253/201707 adopted by PRAC in March 2018

#### 16.4.2. Vemurafenib - ZELBORAF (CAP) - EMEA/H/C/002409/LEG 037.2

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to LEG 037.1 [Review of cases of lymphopenia as requested in the conclusions of PSUSA/00009329/201608 adopted in March 2017] as per the conclusions adopted by PRAC/CHMP in February 2018

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

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

### 17.1. Protocols of PASS imposed in the marketing authorisation(s)<sup>76</sup>

#### 17.1.1. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/PSP/S/0057.1

---

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to PSP/S/0057 [protocol for a cerebrotendinous xanthomatosis registry: a long term non-interventional follow-up of safety and effectiveness of Chenodeoxycholic acid Leadiant (chenodeoxycholic acid)] as per the request for supplementary information (RSI) adopted in February 2018

---

<sup>76</sup> In accordance with Article 107n of Directive 2001/83/EC

#### 17.1.2. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/PSP/S/0065

---

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a registry of patients with high-risk neuroblastoma being treated with Qarziba (dinutuximab beta) to assess: 1) pain severity and use of analgesics during treatment; 2) incidence of neurotoxicity, visual impairment, capillary leak syndrome, cardiovascular events and hypersensitivity reactions; 3) long term safety

#### 17.1.3. Valproate (NAP) - EMEA/H/N/PSA/J/0015.3

---

Applicant: Sanofi-aventis Recherche & Development (on behalf of a consortium)

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to PSA/J/0015.2 [protocol for a joint drug utilisation study (DUS) using EU databases to study the effectiveness of the imposed risk minimisation measures following the conclusion of the referral procedure under Article 31 of Directive 2001/83/EC completed in 2014 (EMA/H/A-31/1387) and to further characterise the prescribing patterns for valproate] as per the request for supplementary information (RSI) adopted in February 2018

### 17.2. Protocols of PASS non-imposed in the marketing authorisation(s)<sup>77</sup>

#### 17.2.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 008.4

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 008.3 [protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per the request for supplementary information (RSI) adopted in March 2018

#### 17.2.2. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 012.3

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 012.2 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as per the request for supplementary information (RSI) adopted in February 2018

---

<sup>77</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

#### 17.2.3. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 013.2

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 013.1 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.2.4. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 007.4

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 007.3 [protocol for a retrospective, observational new user cohort study, using four administrative claims databases in the US, to assess the incidence of diabetic ketoacidosis (DKA) among patients with type 2 diabetes mellitus (T2DM) treated with medicines containing sodium-glucose co-transporter-2 (SGLT2) inhibitors or other antihyperglycemic agents], as per the request for supplementary information (RSI) adopted in March 2018

#### 17.2.5. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 011.3

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 011.3 [PASS protocol for an epidemiological study to evaluate the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly exposed to canagliflozin-containing products compared to patients with T2DM exposed to non-sodium-glucose co-transporter-2 (SGLT2) inhibitor anti-hyperglycaemic agents: a retrospective cohort study using large claims databases in the United States] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.2.6. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 012.2

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 012.1 [PASS protocol for a US epidemiology database study to further characterise the incidence of below-knee lower limb amputation in patients taking canagliflozin (listed as a category 3 study in RMP) as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.2.7. Cladribine - MAVENCLAD (CAP) - EMEA/H/C/004230/MEA 003.1

---

Applicant: Merck Serono Europe Limited

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: MAH's response to MEA 003 [protocol for PASS MS700568-0004 on pregnancy aimed at assessing the occurrence of major congenital abnormalities (MCA), estimating proportions of pregnancy outcomes, proportions of alterations in foetal growth and pre-term births in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine, and comparison of study outcomes with pregnant women with multiple sclerosis (MS) not exposed to any disease modifying drugs (DMDs) [final study report due date: Q1/2028] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.2.8. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/MEA 003.2

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Sabine Straus

Scope: MAH's response to MEA 003.1 [protocol for study ML39302 (COVENIS) (listed as a category 3 study in the RMP): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastases with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.2.9. Daclatasvir - DAKLINZA (CAP) - EMEA/H/C/003768/MEA 019.2

---

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 019.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.10. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 007.2

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of

Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.11. Denosumab - XGEVA (CAP) - EMA/H/C/002173/MEA 026

---

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20170728: a retrospective cohort study to measure the incidence of new primary malignancies among patients with bone metastases from breast, prostate, or lung cancer treated with Xgeva (denosumab) or intravenous zoledronic acid

#### 17.2.12. Elbasvir, grazoprevir - ZEPATIER (CAP) - EMA/H/C/004126/MEA 004.2

---

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 004 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.13. Emicizumab - HEMLIBRA (CAP) - EMA/H/C/004406/MEA 001

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Protocol for a PASS based on the European Haemophilia Safety Surveillance (EUHASS) registry to characterise the safety profile of patients with haemophilia A exposed to emicizumab under real-world conditions, including an estimate of event rates of the following important risks: thromboembolic events, thrombotic microangiopathy, systemic hypersensitivity, anaphylaxis and anaphylactoid events [final clinical study report: (CSR) expected in June 2024] (from initial opinion/MA)

#### 17.2.14. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - EMA/H/C/000594/MEA 045.5

---

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 045.4 [PASS protocol for study GS-EU-276-4027, a drug utilisation study (DUS) to characterize: 1) prescribers' level of knowledge about the key risks of Truvada for a pre-exposure prophylaxis (PrEP) indication and assess the effectiveness of risk minimisation measures; 2) prescribing practices in routine clinical practice of Truvada for PrEP by describing the demographics of human immunodeficiency



virus 1 (HIV-1) uninfected individuals who were prescribed Truvada for PrEP, and the prescribed dosing schedule for Truvada for PrEP as reported by the prescriber] as per the request for supplementary information (RSI) adopted in March 2018

#### 17.2.15. Glecaprevir, pibrentasvir - MAVIRET (CAP) - EMEA/H/C/004430/MEA 006.1

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 006 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.16. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 002

---

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP: a national prospective study to assess long-term toxicity from the use of biological agents to treat patients with rheumatological disorders in routine clinical practice using the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an established nationwide register [final clinical study report expected in 2027] (from initial opinion/MA)

#### 17.2.17. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 005

---

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP: a prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of rheumatoid arthritis (RA) and to compare this to a cohort of RA patients who are treated with non-biologic disease-modifying antirheumatic drugs (DMARDs) using the German Register for Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT<sup>78</sup>) [final clinical study report planned expected in 2027] (from initial opinion/MA)

#### 17.2.18. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/MEA 006

---

Applicant: Samsung Bioepis UK Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for a study listed as a category 3 in the RMP conducted in the Spanish

---

<sup>78</sup> Rheumatoide Arthritis: Beobachtung der Biologika-Therapie

register of adverse events of biological therapies in rheumatic diseases (BIOBADASER<sup>79</sup>) in order to identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, to estimate the frequency of their occurrence; to identify unexpected adverse events; to identify relevant adverse events that occur following the suspension of the treatment, to estimate the relative risk of occurrence of adverse events with biological therapies in patients with rheumatoid arthritis (RA) compared to those not exposed to these treatments; to identify risk factors for suffering adverse reactions with these treatments; to evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment [final clinical study report planned expected in 2027] (from initial opinion/MA)

#### 17.2.19. [Ledipasvir, sofosbuvir - HARVONI \(CAP\) - EMEA/H/C/003850/MEA 017.2](#)

---

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 017.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.20. [Meningococcal group B vaccine \(recombinant, adsorbed\) - TRUMENBA \(CAP\) - EMEA/H/C/004051/MEA 003](#)

---

Applicant: Pfizer Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Protocol for study B1971060: a phase 4, open-label, single-arm trial, to describe the safety, tolerability and immunogenicity of Trumenba (bivalent rLP2086 vaccine) when administered in immunocompromised subjects  $\geq 10$  years of age

#### 17.2.21. [Naloxegol - MOVENTIG \(CAP\) - EMEA/H/C/002810/MEA 006.5](#)

---

Applicant: Kyowa Kirin Limited

PRAC Rapporteur: Almath Spooner

Scope: Amended protocol to a previously agreed protocol (D3820R00009) for study D2288R00084: a naloxegol post-market observational safety study in patients taking opioids for non-cancer pain

#### 17.2.22. [Niraparib - ZEJULA \(CAP\) - EMEA/H/C/004249/MEA 003](#)

---

Applicant: Tesaro UK Limited

---

<sup>79</sup> Registro español de acontecimientos adversos de terapias biológicas en enfermedades reumáticas

PRAC Rapporteur: Patrick Batty

Scope: Protocol and statistical analysis plan for a non-interventional non-imposed PASS: a pooled analysis of the incidence of acute myelogenous leukaemia, myelodysplastic syndrome, and other secondary primary malignancies in patients treated with niraparib

**17.2.23. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 007.2**

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: MAH's response to MEA 007.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

**17.2.24. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 059**

---

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Patrick Batty

Scope: Protocol for study 20170701: an observational study to assess the effectiveness of the Neulasta (pegfilgrastim) patient alert card (PAC) and to measure medication errors related to the use of the on-body injector (OBI) to assess respondent awareness of key safety messages and behavioural intent to carry out recommended actions as described in the PAC and to estimate the proportion of OBI administrations associated with medication error [final study report expected in March 2022] (from variation II/093/G)

**17.2.25. Reslizumab - CINQAERO (CAP) - EMEA/H/C/003912/MEA 004.2**

---

Applicant: Teva Pharmaceuticals Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Amendment to the initially approved PASS protocol in September 2017 for study C38072-AS-50026, a non-interventional phase 4 study active pregnancy surveillance: effect of reslizumab exposure on pregnancy outcomes [final clinical study report (CSR) expected in December 2028]

**17.2.26. Rituximab - MABTHERA (CAP) - EMEA/H/C/000165/MEA 093.7**

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: Updated protocol for study BE29950 [PASS registry protocol for a long-term surveillance study of Mabthera (rituximab)-treated patients with granulomatosis, with polyangiitis (GPA) or microscopic polyangiitis (MPA) (RIVAS)] following the assessment of

the revised statistical analysis plan (SAP) concluded at the November 2017 PRAC/CHMP

#### 17.2.27. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/MEA 024.2

---

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: MAH's response to MEA 024.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.28. Sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/MEA 008.2

---

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 008.1 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

#### 17.2.29. Sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/MEA 002.1

---

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: MAH's response to MEA 002 including a joint protocol [feasibility assessment for a prospective cohort study in hepatitis C virus (HCV) infected patients with compensated cirrhosis (CPT-A) without history of hepatocellular carcinoma (HCC) and treated with direct-acting antivirals (DAAV) using the Veterans Health Administration Cohort (listed as category 3 study in RMP) as requested in the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals (DAAV) indicated for treatment of hepatitis C (interferon-free) completed in December 2016 (EMA/H/A-20/1438)] as per the request for supplementary information (RSI) adopted in January 2018

### 17.3. Results of PASS imposed in the marketing authorisation(s)<sup>80</sup>

None

---

<sup>80</sup> In accordance with Article 107p-q of Directive 2001/83/EC

## **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>81</sup>**

### **17.4.1. Miglustat - ZAVESCA (CAP) - EMEA/H/C/000435/II/0062/G, Orphan**

---

Applicant: Actelion Registration Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report of the ninth Niemann-Pick disease type C (NPC) registry report including an RMP update within the context of variation II/56 finalised at CHMP in July 2017; 2) submission of an updated RMP (version 14) in order to remove the important identified risks: 'reduced platelet counts and weight loss' as requested in the conclusions of the PSUSA procedure for miglustat (EMA/H/C/PSUSA/00002062/201710) adopted by PRAC in May 2018

### **17.4.2. Ranibizumab - LUCENTIS (CAP) - EMEA/H/C/000715/II/0070/G**

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) submission of the final report from the LUMINOUS study (CRFB002A2406): an observational, multicentre study to assess the long term safety and effectiveness of ranibizumab in routine clinical practice, in fulfilment of the post-authorisation measures MEA 036, MEA 048 and MEA 054; The RMP is updated accordingly; 2) submission of an updated RMP (version 17.0) to include changes not consequential to LUMINOUS study. In addition, the MAH is proposing the removal of the use of educational materials and targeted follow-up checklists listed in Annex II-D of the product information

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

### **17.5.1. Aclidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/ANX 001.5**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 001.4 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

### **17.5.2. Aclidinium - EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/ANX 001.5**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

---

<sup>81</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

Scope: MAH's response to ANX 001.4 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.5.3. [Aclidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR \(CAP\) - EMEA/H/C/003969/ANX 003.2](#)

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX 003.1 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.5.4. [Aclidinium, formoterol fumarate dihydrate - DUAKLIR GENUAIR \(CAP\) - EMEA/H/C/003745/ANX 003.2](#)

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: MAH's response to ANX-003.1 [First interim report for imposed study D6560R00004: an observational study evaluating the risk of cardiovascular endpoints of aclidinium bromide-containing products versus other chronic obstructive pulmonary disease (COPD) medications in COPD patients in the UK. The report addresses the all-cause mortality component of the PASS programme] as per the request for supplementary information (RSI) adopted in February 2018

#### 17.5.5. [Ataluren - TRANSLARNA \(CAP\) - EMEA/H/C/002720/MEA 002.3](#)

---

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Sabine Straus

Scope: Three year interim report for study PTC124-GD-025o-DMD (listed as a category 3 study in the RMP): a post-approval registry observational study exploring the long-term of ataluren safety and effectiveness in usual care setting [final clinical study report (CSR) expected in: April 2023]

#### 17.5.6. [Bedaquiline - SIRTURO \(CAP\) - EMEA/H/C/002614/MEA 010.3](#)

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fourth interim results (semi-annual report) for study TMC207TBC4002 (listed as a category 3 study in the RMP): a multi-country prospective multidrug-resistant tuberculosis

(MDRTB) disease registry to monitor bedaquiline safety, utilisation, and emergence of resistance [final study report expected in Q2 2020]

#### 17.5.7. Elosulfase alfa - VIMIZIM (CAP) - EMEA/H/C/002779/ANX 005.3

---

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Patrick Batty

Scope: Fourth annual study report (reporting period: 14 February 2017 to 13 February 2018) for the multicentre, multinational, observational Morquio A registry study (MARS): a voluntary observational registry study to characterise and describe the mucopolysaccharidosis IV type A (MPS IVA) population and to evaluate the long-term effectiveness and safety of Vimizim (elosulfase alfa) (final clinical study report (CSR): March 2025), including the MAH's responses to ANX 005.2 to the request for supplementary information (RSI) adopted in July 2017

#### 17.5.8. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 001.3

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Interim results for study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

#### 17.5.9. Florbetapir (<sup>18</sup>F) - AMYVID (CAP) - EMEA/H/C/002422/MEA 001.5

---

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Martin Huber

Scope: Second interim report for study I6E-MC-AVBE: a non-interventional PASS evaluating the effectiveness of Amyvid (florbetapir (<sup>18</sup>F)) reader training programme

#### 17.5.10. Micafungin - MYCAMINE (CAP) - EMEA/H/C/000734/MEA 013.6

---

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Annual report for study ISN 9463-CL-1401 (period from 01 November 2016 until 31 October 2017): an observational database-assisted comparative multicentre cohort study to investigate the risk of hepatotoxicity and hepatocellular carcinoma, and short and long-term safety of micafungin and other parenteral antifungal agents (MYCOS)



17.5.11. Mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches - VELPHORO (CAP) - EMEA/H/C/002705/MEA 002.7

---

Applicant: Vifor Fresenius Medical Care Renal Pharma France

PRAC Rapporteur: Julie Williams

Scope: Fourth interim report (semi-annual) for study VFMCRP-MEAF-PA21-01-EU (Velphoro Evaluation of Real-life saFety, effectIveness and adherence 'VERIFIE' study): a non-interventional study to investigate the short and long-term real-life safety, effectiveness, and adherence of Velphoro (mixture of polynuclear iron(III)-oxyhydroxide, sucrose and starches) in patients with hyperphosphataemia undergoing haemodialysis or peritoneal dialysis (PD)

17.5.12. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001.3

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Interim results for study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

17.5.13. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 002.3

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

17.5.14. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.3

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: First interim report for study CLCZ696B2015 (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]



#### 17.5.15. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 002

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: Interim results for study CLCZ696B2014 (PASS 1) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to characterize the risk of angioedema and other specific safety events of interest in association with the use of Entresto/Neparvis (sacubitril/valsartan) in adult patients with heart failure [final report expected in Q4/2022]

#### 17.5.16. Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Julie Williams

Scope: First interim report for study CLCZ696B2015 (PASS 3) (listed as a category 3 study in the RMP): a non-interventional post-authorisation European multi-database safety study to assess the risk of myotoxicity, hepatotoxicity and acute pancreatitis in statin-exposed heart failure patients with or without concomitant use of Entresto/Neparvis (sacubitril/valsartan) [final report expected in Q2/2020]

#### 17.5.17. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 024.11

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Patrick Batty

Scope: Eighth annual interim report for study CNT01275PS04007 (pregnancy research initiative) (C0743T): exposure to ustekinumab during pregnancy in patients with psoriasis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers. In addition, the submission includes a summary document on pregnancy outcomes from study CNT01275PS04037: pregnancy exposure registry OTIS (Organisation of Teratology Information Specialists) study conducted in North America on autoimmune diseases in pregnancy; study C0168Z03: a multicentre, prospective, observational PSOLAR (Psoriasis Longitudinal Assessment and Registry) study tracking the long-term safety experience and clinical status of patients with psoriasis who are eligible to receive (or are actively receiving) systemic therapies for psoriasis; and study CNT01275PS04007: a prospective, observational, exposure-based cohort Nordic Pregnancy Registry study analysing maternal and birth outcome data obtained from the Swedish Medical Birth Register (SMBR), Danish Medical Birth Register (DMBR) and Finnish Medical Birth Register (FMBR)

### 17.6. Others

#### 17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 006.9

---

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Bi-annual status report for study DNE3001 (CREDENCE): a randomised, double-

blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (seventh IDMC report dated March 2018)

#### 17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 005.9

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: Bi-annual status report for study DNE3001 (CREDENCE): a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy) from the Independent Data Monitoring Committee (IDMC) (seventh IDMC report dated March 2018)

#### 17.6.3. Dasabuvir - EXVIERA (CAP) - EMEA/H/C/003837/MEA 001.4

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Proposal to terminate study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

#### 17.6.4. Desloratadine - AERIUS (CAP) - EMEA/H/C/000313/MEA 065.3

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

#### 17.6.5. Desloratadine - AZOMYR (CAP) - EMEA/H/C/000310/MEA 065.3

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

#### 17.6.6. Desloratadine - NEOCLARITYN (CAP) - EMEA/H/C/000314/MEA 065.3

---

Applicant: Merck Sharp & Dohme Limited

PRAC Rapporteur: Jean-Michel Dogné

Scope: Status update and study milestones for a Nordic register-based study exploring the association between the use of desloratadine and the risk of seizures, supraventricular tachycardia, and atrial fibrillation or flutter

#### 17.6.7. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/MEA 005

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Julie Williams

Scope: PASS protocol for study WA40404 (listed as category 3 study in the RMP): a phase 3b multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis later in their disease course

#### 17.6.8. Ombitasvir, paritaprevir, ritonavir - VIEKIRAX (CAP) - EMEA/H/C/003839/MEA 001.4

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Dolores Montero Corominas

Scope: Proposal to terminate study P15-421: a prospective, observational cohort study utilising the hepatitis C therapeutic registry and research network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of grade 3+ alanine transaminase (ALT) elevations in patients being treated for hepatitis C with paritaprevir with ritonavir (paritaprevir/ritonavir), ombitasvir and dasabuvir (2 direct-acting antiviral (DAA) regimen) or paritaprevir/ritonavir and ombitasvir (3-DAA regimen) with or without ribavirin for hepatitis C infection (HCV) (SHORT – evaluation of the potential for and clinical impact of increased ALT in patients using the AbbVie 2-DAA or 3-DAA regimens in a real world setting

### 17.7. New Scientific Advice

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

### 17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

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

#### **18.1.1. Amifampridine - FIRDAPSE (CAP) - EMEA/H/C/001032/S/0053 (without RMP)**

Applicant: BioMarin Europe Ltd

PRAC Rapporteur: Julie Williams

Scope: Annual reassessment of the marketing authorisation

#### **18.1.2. Chenodeoxycholic acid - CHENODEOXYCHOLIC ACID LEADIANT (CAP) - EMEA/H/C/004061/S/0006 (without RMP)**

Applicant: Leadiant GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Annual reassessment of the marketing authorisation

#### **18.1.3. Dinutuximab beta - QARZIBA (CAP) - EMEA/H/C/003918/S/0006 (without RMP)**

Applicant: EUSA Pharma (UK) Limited

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Annual reassessment of the marketing authorisation

#### **18.1.4. Idursulfase - ELAPRASE (CAP) - EMEA/H/C/000700/S/0075 (without RMP)**

Applicant: Shire Human Genetic Therapies AB

PRAC Rapporteur: Patrick Batty

Scope: Annual reassessment of the marketing authorisation

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

#### **18.2.1. Brentuximab vedotin - ADCETRIS (CAP) - EMEA/H/C/002455/R/0058 (without RMP)**

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

#### **18.2.2. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/R/0012 (without RMP)**

---

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

#### **18.2.3. Olaratumab - LARTRUVO (CAP) - EMEA/H/C/004216/R/0010 (without RMP)**

---

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Sabine Straus

Scope: Conditional renewal of the marketing authorisation

#### **18.2.4. Venetoclax - VENCLYXTO (CAP) - EMEA/H/C/004106/R/0013 (without RMP)**

---

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Patrick Batty

Scope: Conditional renewal of the marketing authorisation

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

#### **18.3.1. Dapagliflozin, metformin - XIGDUO (CAP) - EMEA/H/C/002672/R/0044 (without RMP)**

---

Applicant: AstraZeneca AB

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

#### **18.3.2. Dolutegravir - TIVICAY (CAP) - EMEA/H/C/002753/R/0040 (with RMP)**

---

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

#### **18.3.3. Filgrastim - GRAFTOFIL (CAP) - EMEA/H/C/002150/R/0020 (without RMP)**

---

Applicant: Apotex Europe BV

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

#### **18.3.4. Florbetaben (<sup>18</sup>F) - NEURACEQ (CAP) - EMEA/H/C/002553/R/0025 (with RMP)**

---

Applicant: Life Radiopharma Berlin GmbH

PRAC Rapporteur: Patrick Batty

Scope: 5-year renewal of the marketing authorisation

18.3.5. [Levetiracetam - LEVETIRACETAM HOSPIRA \(CAP\) - EMEA/H/C/002783/R/0018 \(without RMP\)](#)

---

Applicant: Hospira UK Limited

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

18.3.6. [Lidocaine, prilocaine - FORTACIN \(CAP\) - EMEA/H/C/002693/R/0023 \(with RMP\)](#)

---

Applicant: Recordati Ireland Ltd

PRAC Rapporteur: Dolores Montero Corominas

Scope: 5-year renewal of the marketing authorisation

18.3.7. [Sofosbuvir - SOVALDI \(CAP\) - EMEA/H/C/002798/R/0050 \(with RMP\)](#)

---

Applicant: Gilead Sciences International Limited

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.8. [Stiripentol - DIACOMIT \(CAP\) - EMEA/H/C/000664/R/0021 \(without RMP\)](#)

---

Applicant: BIOCODEX

PRAC Rapporteur: Julie Williams

Scope: 5-year renewal of the marketing authorisation

18.3.9. [Trastuzumab emtansine - KADCYLA \(CAP\) - EMEA/H/C/002389/R/0039 \(without RMP\)](#)

---

Applicant: Roche Registration GmbH

PRAC Rapporteur: Doris Stenver

Scope: 5-year renewal of the marketing authorisation

18.3.10. [Travoprost - IZBA \(CAP\) - EMEA/H/C/002738/R/0011 \(without RMP\)](#)

---

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Almath Spooner

Scope: 5-year renewal of the marketing authorisation

18.3.11. [Vortioxetine - BRINTELLIX \(CAP\) - EMEA/H/C/002717/R/0019 \(with RMP\)](#)

---

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: 5-year renewal of the marketing authorisation

## 19. Annex II – List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 9-12 July 2018 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 interests declared	Full involvement
Laurence Defays	Alternate	Belgium	No interests declared	Full involvement
Yuliyana Eftimov	Alternate	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Doris Stenver	Member	Denmark	No interests declared	Full involvement
Anette Stark	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				(NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452 4.3.1. Fluoroquinolones: ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP)
Caroline Laborde	Alternate	France	No interests declared	Full involvement
Martin Huber	Member	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislowski	Alternate	Germany	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No participation in discussion, final deliberations and voting on:	4.3.6. Hydrochlorothiazide (NAP); aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA



Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Guðrún Stefánsdóttir	Member	Iceland	No restrictions applicable to this meeting	Full involvement
Almath Spooner	Member (Vice-Chair)	Ireland	No interests declared	Full involvement
Rhea Fitzgerald	Alternate	Ireland	No restrictions applicable to this meeting	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Jolanta Gulbinovic	Member	Lithuania	No interests	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			declared	
Marcel Bruch	Member	Luxembourg	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
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	3.2.1. Fluoroquinolones for systemic and inhalation use: ciprofloxacin (NAP); enoxacin (NAP); flumequin (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) Quinolones for systemic and inhalation use: cinoxacin (NAP); nalidixic acid (NAP); pipemidic acid (NAP) - EMEA/H/A-31/1452 3.3.1. Radium (223Ra) dichloride - XOFIGO (CAP) - EMEA/H/A-20/1459 4.3.1. Fluoroquinolones: ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rufloxacin (NAP) 4.3.4. Hormonal contraceptives : chlormadinone acetate, ethinylestradiol (NAP); cyproterone, ethinylestradiol (NAP); cyproterone acetate, estradiol valerate (NAP); desogestrel (NAP); desogestrel, ethinylestradiol (NAP); dienogest, estradiol (NAP); dienogest, ethinylestradiol (NAP); drospirenone, ethinylestradiol (NAP); estradiol, nomegestrol acetate - ZOELY (CAP), NAP; ethinylestradiol, etonogestrel (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, gestodene (NAP); ethinylestradiol, levonorgestrel (NAP); ethinyl

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				estradiol, norelgestromin - EVRA (CAP), NAP; ethinylestradiol, norethisterone (NAP); ethinylestradiol, norgestimate (NAP); ethinylestradiol, norgestrel (NAP); levonorgestrel, ethinylestradiol; ethinylestradiol (NAP); levonorgestrel (NAP); medroxyprogesterone (NAP); norethisterone (NAP) 4.3.6. Hydrochlorothiazide (NAP); aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP); amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP); amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP); irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				AZIDE TEVA (CAP), KARVEZIDE (CAP); telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP) 11.1.1. Dienogest, estradiol valerate (NAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Milena Radoha-Bergoč	Member	Slovenia	No participation in final deliberations and voting on:	4.3.1. Fluoroquinolones: ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP);

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				<p>rufloxacin (NAP)</p> <p>4.3.6.</p> <p>Hydrochlorothiazide (NAP);</p> <p>aliskiren, hydrochlorothiazide – RASILEZ HCT (CAP);</p> <p>amlodipine, valsartan, hydrochlorothiazide – COPALIA HCT (CAP);</p> <p>amlodipine besylate, valsartan, hydrochlorothiazide – DAFIRO HCT (CAP), EXFORGE HCT (CAP);</p> <p>irbesartan, hydrochlorothiazide – COAPROVEL (CAP), IFIRMACOMBI (CAP), IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP), IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP), KARVEZIDE (CAP);</p> <p>telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP)</p> <p>6.3.28.</p> <p>Rosuvastatin (NAP)</p>
Dolores Montero Corominas	Member	Spain	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
Eva Segovia	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate-via telephone*	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No participation in final deliberations and voting on:	4.3.1. Fluoroquinolone s: ciprofloxacin (NAP); enoxacin (NAP); flumequine (NAP); levofloxacin – QUINSAIR (CAP), NAP; lomefloxacin (NAP); moxifloxacin (NAP); norfloxacin (NAP); ofloxacin (NAP); pefloxacin (NAP); prulifloxacin (NAP); rifloxacin (NAP)
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Kirsten Myhr	Alternate	Healthcare Professionals' Representative	No interests declared	Full involvement
Albert van der Zeijden	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Doris Hovgaard	Expert - in person*	Denmark	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
Nadia Achab	Expert - via telephone*	France	No interests declared	Full involvement
Mathilde Geynet-Kovacs	Expert - via telephone*	France	No interests declared	Full involvement
Emilie Monzon	Expert - via telephone*	France	No interests declared	Full involvement
Nathalie Richard	Expert - via telephone*	France	No interests declared	Full involvement
Thomas Gröger	Expert - via telephone*	Germany	No interests declared	Full involvement
Franziska Heinrich	Expert - via telephone*	Germany	No interests declared	Full involvement
Nils Lilienthal	Expert - in person*	Germany	No interests declared	Full involvement
Walburga Lütkehermölle	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Christoph Unkrig	Expert - in person*	Germany	No interests declared	Full involvement
Florianne Bauer	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Ineke Crijns	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Frederika Adriana van Nimwegen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Elizabeth van Vlijmen	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Pilar Rayón Iglesias	Expert - in person*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Bertil Jonsson	Expert - via telephone*	Sweden	No interests declared	Full involvement
Marta Busana	Expert - in person*	United Kingdom	No interests declared	Full involvement
Mattia Calissano	Expert - in person*	United Kingdom	No interests declared	Full involvement
Ross Hawkes	Expert - in person*	United Kingdom	No restrictions applicable to this meeting	Full involvement
Shahin Kauser	Expert - in person*	United Kingdom	No interests declared	Full involvement
Max Lagnado	Expert - in person*	United Kingdom	No interests declared	Full involvement
Andrew Ruddick	Expert - via telephone*	United Kingdom	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				



\* Experts were only evaluated against the agenda topics or activities they participated in

## 20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

## 21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

### **EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures**

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WCOB01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WCOB01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

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

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

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

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

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

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