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## Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting on 26 – 29 October 2020

Chair: Sabine Straus – Vice-Chair: Martin Huber

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

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## Table of contents

<b>1.</b>	<b>Introduction</b>	<b>11</b>
1.1.	Welcome and declarations of interest of members, alternates and experts .....	11
1.2.	Agenda of the meeting on 26 – 29 October 2020 .....	11
1.3.	Minutes of the previous meeting on 28 September – 01 October 2020 .....	11
<b>2.</b>	<b>EU referral procedures for safety reasons: urgent EU procedures</b>	<b>11</b>
2.1.	Newly triggered procedures .....	11
2.2.	Ongoing procedures .....	12
2.3.	Procedures for finalisation.....	12
<b>3.</b>	<b>EU referral procedures for safety reasons: other EU referral procedures</b>	<b>12</b>
3.1.	Newly triggered procedures .....	12
3.2.	Ongoing procedures .....	12
3.2.1.	Ifosfamide (NAP) - EMEA/H/A-31/1495 .....	12
3.3.	Procedures for finalisation.....	12
3.4.	Re-examination procedures.....	12
3.5.	Others .....	13
<b>4.</b>	<b>Signals assessment and prioritisation</b>	<b>13</b>
4.1.	New signals detected from EU spontaneous reporting systems .....	13
4.1.1.	Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP); avelumab – BAVENCIO (CAP); cemiplimab – LIBTAYO (CAP); durvalumab – IMFINZI (CAP); ipilimumab – YERVOY (CAP); pembrolizumab – KEYTRUDA (CAP); nivolumab - OPDIVO (CAP) .....	13
4.2.	New signals detected from other sources .....	15
4.2.1.	Cannabidiol – EPIDYOLEX (CAP); tacrolimus - ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP); NAP .....	15
4.3.	Signals follow-up and prioritisation.....	16
4.3.1.	Anakinra - KINERET (CAP) - EMEA/H/C/000363/SDA/032; canakinumab - ILARIS (CAP) - EMEA/H/C/001109/SDA/054 .....	16
4.3.2.	Cefepime (NAP).....	17
4.3.3.	Ceftriaxone (NAP).....	18
4.3.4.	Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/SDA/018; trametinib - MEKINIST (CAP) - EMEA/H/C/002643/SDA/013 .....	18
4.3.5.	Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/SDA/031 .....	19
4.3.6.	Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP) – EMEA/H/C/004143/SDA/020; avelumab – BAVENCIO (CAP) – EMEA/H/C/004338/SDA/006; cemiplimab – LIBTAYO (CAP) - EMEA/H/C/004844/SDA/006; durvalumab – IMFINZI (CAP) - EMEA/H/C/004771/SDA/006; ipilimumab – YERVOY (CAP) – EMEA/H/C/002213/SDA/040; pembrolizumab – KEYTRUDA (CAP) - EMEA/H/C/003820/SDA/026; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/SDA/041 .....	20

4.3.7.	Lamotrigine (NAP) .....	20
<b>4.4.</b>	<b>Variation procedure(s) resulting from signal evaluation .....</b>	<b>21</b>
4.4.1.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0019.....	21
<b>5.</b>	<b>Risk management plans (RMPs) .....</b>	<b>22</b>
<b>5.1.</b>	<b>Medicines in the pre-authorisation phase .....</b>	<b>22</b>
5.1.1.	Estetrol, drospirenone - EMEA/H/C/005336.....	22
5.1.2.	Estetrol, drospirenone - EMEA/H/C/005382.....	22
5.1.3.	Lisocabtagene maraleucel - EMEA/H/C/004731, Orphan .....	22
5.1.4.	Risdiplam - EMEA/H/C/005145, Orphan.....	22
<b>5.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures.....</b>	<b>22</b>
<b>5.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures .....</b>	<b>22</b>
5.3.1.	Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/X/0116 .....	23
<b>6.</b>	<b>Periodic safety update reports (PSURs) .....</b>	<b>23</b>
<b>6.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only .....</b>	<b>23</b>
6.1.1.	Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/202004 .....	24
6.1.2.	Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/202003 .....	24
6.1.3.	Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202003 .....	25
6.1.4.	Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/202003 .....	26
6.1.5.	Ipilimumab - YERVOY (CAP) - PSUSA/00009200/202003 .....	27
6.1.6.	Nintedanib - OFEV (CAP) - PSUSA/00010319/202004 .....	28
6.1.7.	Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/202003 .....	28
6.1.8.	Siponimod - MAYZENT (CAP) - PSUSA/00010818/202003 (with RMP) .....	29
6.1.9.	Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202003 .....	30
<b>6.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....</b>	<b>31</b>
6.2.1.	Enoxaparin - INHIXA (CAP); NAP - PSUSA/00010833/202004 .....	31
6.2.2.	Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP); VIREAD (CAP); NAP - PSUSA/00002892/202003.....	31
6.2.3.	Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/202003 .....	32
<b>6.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>33</b>
6.3.1.	Ethosuximide (NAP) - PSUSA/00001316/202003 .....	33
6.3.2.	Flucloxacillin (NAP) - PSUSA/00001402/202003 .....	34
6.3.3.	Fluconazole (NAP) - PSUSA/00001404/202003.....	35
6.3.4.	Galantamine (NAP) - PSUSA/00001512/202003 .....	35
6.3.5.	Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202003.....	36
6.3.6.	Lanthanum (NAP) - PSUSA/00003175/202003 .....	37

6.3.7.	Metamizole (NAP) - PSUSA/00001997/202003 .....	37
<b>6.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>38</b>
<b>6.5.</b>	<b>Variation procedure(s) resulting from PSUSA evaluation .....</b>	<b>39</b>
6.5.1.	Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0022, Orphan .....	39
<b>6.6.</b>	<b>Expedited summary safety reviews .....</b>	<b>39</b>
6.6.1.	Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.3 .....	39
<b>7.</b>	<b>Post-authorisation safety studies (PASS) .....</b>	<b>40</b>
7.1.	Protocols of PASS imposed in the marketing authorisation(s).....	40
7.2.	Protocols of PASS non-imposed in the marketing authorisation(s) .....	40
7.3.	Results of PASS imposed in the marketing authorisation(s).....	40
7.4.	Results of PASS non-imposed in the marketing authorisation(s).....	40
7.5.	Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation.....	40
7.6.	Others .....	41
7.7.	New Scientific Advice .....	41
7.8.	Ongoing Scientific Advice .....	41
7.9.	Final Scientific Advice (Reports and Scientific Advice letters) .....	41
<b>8.</b>	<b>Renewals of the marketing authorisation, conditional renewal and annual reassessments .....</b>	<b>41</b>
8.1.	Annual reassessments of the marketing authorisation .....	41
8.2.	Conditional renewals of the marketing authorisation .....	41
8.3.	Renewals of the marketing authorisation .....	41
<b>9.</b>	<b>Product related pharmacovigilance inspections .....</b>	<b>41</b>
9.1.	List of planned pharmacovigilance inspections.....	41
9.2.	Ongoing or concluded pharmacovigilance inspections.....	41
9.3.	Others .....	41
<b>10.</b>	<b>Other safety issues for discussion requested by the CHMP or EMA .....</b>	<b>42</b>
10.1.	Safety related variations of the marketing authorisation.....	42
10.2.	Timing and message content in relation to Member States' safety announcements .....	42
10.3.	Other requests.....	42
10.4.	Scientific Advice .....	42
<b>11.</b>	<b>Other safety issues for discussion requested by the Member States .....</b>	<b>42</b>
11.1.	Safety related variations of the marketing authorisation.....	42
11.2.	Other requests.....	42
<b>12.</b>	<b>Organisational, regulatory and methodological matters .....</b>	<b>42</b>
12.1.	Mandate and organisation of the PRAC.....	42

<b>12.2.</b>	<b>Coordination with EMA Scientific Committees or CMDh-v .....</b>	<b>42</b>
<b>12.3.</b>	<b>Coordination with EMA Working Parties/Working Groups/Drafting Groups .....</b>	<b>42</b>
<b>12.4.</b>	<b>Cooperation within the EU regulatory network .....</b>	<b>43</b>
12.4.1.	Coronavirus (COVID-19) pandemic - update .....	43
12.4.2.	Coronavirus (COVID-19) pandemic – pharmacovigilance initiatives: preparedness plan and coverage data gathering .....	43
12.4.3.	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group – Call for expression of interest for a PRAC representative.....	43
<b>12.5.</b>	<b>Cooperation with International Regulators.....</b>	<b>43</b>
<b>12.6.</b>	<b>Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee .....</b>	<b>43</b>
<b>12.7.</b>	<b>PRAC work plan .....</b>	<b>43</b>
<b>12.8.</b>	<b>Planning and reporting .....</b>	<b>44</b>
12.8.1.	EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q3 2020 and predictions.....	44
<b>12.9.</b>	<b>Pharmacovigilance audits and inspections .....</b>	<b>44</b>
12.9.1.	Pharmacovigilance systems and their quality systems .....	44
12.9.2.	Pharmacovigilance inspections .....	44
12.9.3.	Pharmacovigilance audits.....	44
<b>12.10.</b>	<b>Periodic safety update reports (PSURs) &amp; Union reference date (EURD) list .....</b>	<b>44</b>
12.10.1.	Periodic safety update reports .....	44
12.10.2.	Granularity and Periodicity Advisory Group (GPAG) .....	44
12.10.3.	PSURs repository .....	44
12.10.4.	Union reference date list – consultation on the draft list .....	44
12.10.5.	Union reference date (EURD) list – EURD tool.....	45
<b>12.11.</b>	<b>Signal management .....</b>	<b>45</b>
12.11.1.	Signal management – feedback from Signal Management Review Technical (SMART) Working Group .....	45
<b>12.12.</b>	<b>Adverse drug reactions reporting and additional monitoring .....</b>	<b>45</b>
12.12.1.	Management and reporting of adverse reactions to medicinal products.....	45
12.12.2.	Additional monitoring .....	45
12.12.3.	List of products under additional monitoring – consultation on the draft list .....	45
<b>12.13.</b>	<b>EudraVigilance database.....</b>	<b>46</b>
12.13.1.	Activities related to the confirmation of full functionality .....	46
12.13.2.	EudraVigilance – Expert Working Group (EV-EWG) - work programme 2021-2022 .....	46
<b>12.14.</b>	<b>Risk management plans and effectiveness of risk minimisations.....</b>	<b>46</b>
12.14.1.	Coronavirus (COVID-19) pandemic - coreRMP19 guidance and requirements for COVID-19 vaccines .....	46
12.14.2.	Risk management systems .....	46
12.14.3.	Tools, educational materials and effectiveness measurement of risk minimisations .....	46

<b>12.15.</b>	<b>Post-authorisation safety studies (PASS)</b> .....	<b>46</b>
12.15.1.	Post-authorisation Safety Studies – imposed PASS .....	46
12.15.2.	Post-authorisation Safety Studies – non-imposed PASS .....	46
<b>12.16.</b>	<b>Community procedures</b> .....	<b>47</b>
12.16.1.	Referral procedures for safety reasons .....	47
<b>12.17.</b>	<b>Renewals, conditional renewals, annual reassessments</b> .....	<b>47</b>
<b>12.18.</b>	<b>Risk communication and transparency</b> .....	<b>47</b>
12.18.1.	Public participation in pharmacovigilance .....	47
12.18.2.	Safety communication .....	47
<b>12.19.</b>	<b>Continuous pharmacovigilance</b> .....	<b>47</b>
12.19.1.	Incident management .....	47
<b>12.20.</b>	<b>Others</b> .....	<b>47</b>
12.20.1.	Good Pharmacovigilance Practice (GVP) - update on GVP status overview – planning for 2021 .....	47
12.20.2.	Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – Revised process for prioritising impact research topics.....	47
<b>13.</b>	<b>Any other business</b> .....	<b>48</b>
<b>14.</b>	<b>Annex I – Signals assessment and prioritisation</b> .....	<b>48</b>
<b>14.1.</b>	<b>New signals detected from EU spontaneous reporting systems</b> .....	<b>48</b>
<b>14.2.</b>	<b>New signals detected from other sources</b> .....	<b>48</b>
14.2.1.	Trastuzumab emtansine – KADCYLA (CAP).....	48
<b>15.</b>	<b>Annex I – Risk management plans</b> .....	<b>48</b>
<b>15.1.</b>	<b>Medicines in the pre-authorisation phase</b> .....	<b>48</b>
15.1.1.	Adalimumab - EMEA/H/C/005188 .....	48
15.1.2.	Bevacizumab - EMEA/H/C/005640 .....	49
<b>15.2.</b>	<b>Medicines in the post-authorisation phase – PRAC-led procedures</b> .....	<b>49</b>
15.2.1.	Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/WS1849/0045; VALDOXAN (CAP) - EMEA/H/C/000915/WS1849/0047.....	49
15.2.2.	Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/II/0040.....	49
15.2.3.	Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/II/0066 .....	50
15.2.4.	Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/II/0042, Orphan.....	50
15.2.5.	Pramipexole - MIRAPEXIN (CAP) - EMEA/H/C/000134/WS1897/0096; SIFROL (CAP) - EMEA/H/C/000133/WS1897/0087.....	50
15.2.6.	Tacrolimus - ADVAGRAF (CAP) - EMEA/H/C/000712/WS1805/0057; MODIGRAF (CAP) - EMEA/H/C/000954/WS1805/0035; NAP.....	51
15.2.7.	Tolvaptan - JINARC (CAP) - EMEA/H/C/002788/II/0029 .....	51
15.2.8.	Trabectedin - YONDELIS (CAP) - EMEA/H/C/000773/II/0061.....	51
15.2.9.	Umeclidinium bromide - INCRUSE ELLIPTA (CAP) - EMEA/H/C/002809/WS1589/0029; ROLUFTA ELLIPTA (CAP) - EMEA/H/C/004654/WS1589/0014 .....	51
<b>15.3.</b>	<b>Medicines in the post-authorisation phase – CHMP-led procedures</b> .....	<b>52</b>

15.3.1.	Avatrombopag - DOPTelet (CAP) - EMEA/H/C/004722/II/0004/G .....	52
15.3.2.	Beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium - TRIMBOW (CAP) - EMEA/H/C/004257/X/0008/G.....	52
15.3.3.	Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0070.....	52
15.3.4.	Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0045, Orphan .....	53
15.3.5.	Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA (CAP) - EMEA/H/C/004781/X/0014/G.....	53
15.3.6.	Fluticasone furoate, umeclidinium, vilanterol - TEMYBRIC ELLIPTA (CAP) - EMEA/H/C/005254/X/0004/G.....	53
15.3.7.	Fluticasone furoate, umeclidinium, vilanterol - TRELEGY ELLIPTA (CAP) - EMEA/H/C/004363/X/0012/G.....	53
15.3.8.	Follitropin delta - REKOVELLE (CAP) - EMEA/H/C/003994/II/0022 .....	54
15.3.9.	Ipilimumab - YERVOY (CAP) - EMEA/H/C/002213/WS1840/0084; nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/WS1840/0089 .....	54
15.3.10.	Lacosamide - LACOSAMIDE ACCORD (CAP) - EMEA/H/C/004443/X/0007.....	54
15.3.11.	Lipegfilgrastim - LONQUEx (CAP) - EMEA/H/C/002556/II/0058/G.....	54
15.3.12.	Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/II/0035/G .....	54
15.3.13.	Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0021 .....	55
15.3.14.	Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/II/0098/G.....	55
15.3.15.	Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1893/0034; RITEMVIA (CAP) - EMEA/H/C/004725/WS1893/0034; TRUXIMA (CAP) - EMEA/H/C/004112/WS1893/0037... ..	55
15.3.16.	Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/X/0074/G .....	56
15.3.17.	Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0020 .....	56
15.3.18.	Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS1830/0032; NEPARVIS (CAP) - EMEA/H/C/004343/WS1830/0029 .....	56
15.3.19.	Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0026 .....	57
15.3.20.	Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0028 .....	57
15.3.21.	Stiripentol - DIACOMIT (CAP) - EMEA/H/C/000664/X/0032.....	57

## **16. Annex I - Periodic safety update reports (PSURs) 57**

<b>16.1.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only.....</b>	<b>57</b>
16.1.1.	Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202003.....	57
16.1.2.	Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202003 .....	58
16.1.3.	Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202004 .....	58
16.1.4.	Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202003 .....	58
16.1.5.	Certolizumab - CIMZIA (CAP) - PSUSA/00000624/202003 .....	58
16.1.6.	Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202003 .....	58
16.1.7.	Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202004 .....	58
16.1.8.	Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202003 .....	58
16.1.9.	Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/202004.....	59
16.1.10.	Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/202004.....	59

16.1.11.	Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/202004 .....	59
16.1.12.	Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202004.....	59
16.1.13.	Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202003 .....	59
16.1.14.	Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202003 .....	59
16.1.15.	Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202004 .....	59
16.1.16.	Histamine - CEPLENE (CAP) - PSUSA/00001610/202004 .....	60
16.1.17.	Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/202004 .....	60
16.1.18.	Ixekizumab - TALTZ (CAP) - PSUSA/00010493/202003 .....	60
16.1.19.	Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202003 .....	60
16.1.20.	Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202003 .....	60
16.1.21.	Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to <i>Corynebacterium diphtheriae</i> CRM <sub>197</sub> protein) - MENVEO (CAP) - PSUSA/00001969/202003 .....	60
16.1.22.	Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202003 .....	60
16.1.23.	Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202003 .....	61
16.1.24.	Niraparib - ZEJULA (CAP) - PSUSA/00010655/202003.....	61
16.1.25.	Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202003 .....	61
16.1.26.	Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/202003 .....	61
16.1.27.	Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202004 .....	61
16.1.28.	Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/202003 .....	61
16.1.29.	Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/202004.....	61
16.1.30.	Yttrium ( <sup>90</sup> Y) chloride - YTRACIS (CAP); YTRIGA (CAP) - PSUSA/00003137/202003 .....	62
<b>16.2.</b>	<b>PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs).....</b>	<b>62</b>
<b>16.3.</b>	<b>PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only.....</b>	<b>62</b>
16.3.1.	Ascorbic acid, paracetamol, pheniramine maleate (NAP) - PSUSA/00002368/202003 .....	62
16.3.2.	Trandolapril, verapamil (NAP) - PSUSA/00003005/202003.....	62
<b>16.4.</b>	<b>Follow-up to PSUR/PSUSA procedures .....</b>	<b>62</b>
16.4.1.	Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/LEG 050 .....	62

## **17. Annex I – Post-authorisation safety studies (PASS) 62**

<b>17.1.</b>	<b>Protocols of PASS imposed in the marketing authorisation(s).....</b>	<b>63</b>
17.1.1.	Betibeglogene autotemcel – ZYNTEGLO (CAP) - EMEA/H/C/PSA/S/0059 .....	63
17.1.2.	Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSA/S/0054.1.....	63
17.1.3.	Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.5 .....	63
17.1.4.	Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053.1 .....	63
<b>17.2.</b>	<b>Protocols of PASS non-imposed in the marketing authorisation(s) .....</b>	<b>64</b>
17.2.1.	Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.1.....	64
17.2.2.	Interferon beta-1a - AVONEX (CAP) - EMEA/H/C/000102/MEA 088.1 .....	64



17.2.3.	Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/MEA 045.1 .....	64
17.2.4.	Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/MEA 025.1 .....	64
17.2.5.	Interferon beta-1b - EXTAVIA (CAP) - EMEA/H/C/000933/MEA 023.1 .....	64
17.2.6.	Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 004 .....	65
17.2.7.	Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/MEA 010.1 .....	65
17.2.8.	Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.1 .....	65
17.2.9.	Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 002.....	65
17.2.10.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 015.1 .....	65
<b>17.3.</b>	<b>Results of PASS imposed in the marketing authorisation(s).....</b>	<b>66</b>
<b>17.4.</b>	<b>Results of PASS non-imposed in the marketing authorisation(s).....</b>	<b>66</b>
17.4.1.	Acidinium - BRETARIS GENUAIR (CAP) - EMEA/H/C/002706/WS1795/0043; EKLIRA GENUAIR (CAP) - EMEA/H/C/002211/WS1795/0043 .....	66
17.4.2.	Acidinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMEA/H/C/003969/WS1794/0029; DUAKLIR GENUAIR (CAP) - EMEA/H/C/003745/WS1794/0029.....	66
17.4.3.	Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0017.....	66
17.4.4.	Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/WS1923/0068; VOTUBIA (CAP) - EMEA/H/C/002311/WS1923/0067.....	67
17.4.5.	Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1915/0091; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1915/0051; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS1915/0043.....	67
17.4.6.	Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0033.....	67
17.4.7.	Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/II/0054 .....	67
17.4.8.	Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0023.....	68
<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>68</b>
17.5.1.	Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 003 .....	68
17.5.2.	Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 004 .....	68
17.5.3.	Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.4 .....	68
17.5.4.	Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.1 .....	69
17.5.5.	Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.4.....	69
17.5.6.	Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 007.5.....	69
17.5.7.	Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.8.....	69
17.5.8.	Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.8 .....	69
17.5.9.	Sacubitril, valsartan - NEPARVIS (CAP) - EMEA/H/C/004343/MEA 003.5.....	70
17.5.10.	Simoctocog alfa - NUWIQ (CAP) - EMEA/H/C/002813/MEA 004.6.....	70
17.5.11.	Simoctocog alfa - VIHUMA (CAP) - EMEA/H/C/004459/MEA 004.5 .....	70
17.5.12.	Ulipristal acetate - ESMYA (CAP) - EMEA/H/C/002041/MEA 018.4 .....	70
17.5.13.	Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/MEA 001.1 .....	71
<b>17.6.</b>	<b>Others .....</b>	<b>71</b>
<b>17.7.</b>	<b>New Scientific Advice .....</b>	<b>71</b>

<b>17.8.</b>	<b>Ongoing Scientific Advice .....</b>	<b>71</b>
<b>17.9.</b>	<b>Final Scientific Advice (Reports and Scientific Advice letters) .....</b>	<b>71</b>
<b>18.</b>	<b>Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments</b>	<b>71</b>
<b>18.1.</b>	<b>Annual reassessments of the marketing authorisation .....</b>	<b>71</b>
18.1.1.	Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0028 (without RMP) .....	71
18.1.2.	Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0083 (without RMP) .....	72
18.1.3.	Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0051 (without RMP).....	72
18.1.4.	Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0054 (without RMP) .....	72
18.1.5.	Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0017 (without RMP) .....	72
<b>18.2.</b>	<b>Conditional renewals of the marketing authorisation .....</b>	<b>72</b>
18.2.1.	Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0040 (without RMP).....	72
18.2.2.	Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0023 (without RMP).....	72
<b>18.3.</b>	<b>Renewals of the marketing authorisation .....</b>	<b>72</b>
18.3.1.	Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/R/0047 (without RMP).....	72
18.3.2.	Amlodipine, valsartan - AMLODIPINE-VALSARTAN MYLAN (CAP) - EMEA/H/C/004037/R/0008 (with RMP) .....	73
18.3.3.	Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/R/0077 (without RMP) .....	73
18.3.4.	Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/R/0049 (with RMP) .....	73
18.3.5.	Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/R/0051 (without RMP) .....	73
18.3.6.	Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/R/0064 (without RMP).....	73
18.3.7.	Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/R/0027 (with RMP) .....	73
<b>19.</b>	<b>Annex II – List of participants</b>	<b>74</b>
<b>20.</b>	<b>Annex III - List of acronyms and abbreviations</b>	<b>79</b>
<b>21.</b>	<b>Explanatory notes</b>	<b>79</b>

## 1. Introduction

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

The Chairperson opened the 26 - 29 October 2020 meeting by welcoming all participants. Due to the current coronavirus (COVID-19 outbreak), and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

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 (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 revision 2 of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.2](#)). All decisions taken at this meeting held under the conditions of an emergency situation, the Agency's BCP and in compliance with internal guidelines were made in the presence of a quorum of members (i.e. 18 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Nadine Petitpain as the new member for Luxembourg.

### 1.2. Agenda of the meeting on 26 – 29 October 2020

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

### 1.3. Minutes of the previous meeting on 28 September – 01 October 2020

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

Post-meeting note: the PRAC minutes of the meeting held on 28 September – 01 October 2020 were published on the EMA website on 31 December 2020 ([EMA/PRAC/708023/2020](#)).

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

### 2.1. Newly triggered procedures

None

## 2.2. Ongoing procedures

None

## 2.3. Procedures for finalisation

None

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

### 3.1. Newly triggered procedures

None

### 3.2. Ongoing procedures

#### 3.2.1. Ifosfamide<sup>1</sup> (NAP) - EMEA/H/A-31/1495

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Applicant(s): various

PRAC Rapporteur: Martin Huber; PRAC Co-rapporteur: Nikica Mirošević Skvrce

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

#### **Background**

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for the review of ifosfamide solution and concentrate for solution following epidemiological studies suggesting an increased risk of ifosfamide-induced encephalopathy with ifosfamide EG (ifosfamide) solution for infusion compared with ifosfamide powder. For further background, see [PRAC minutes March 2020](#) and [PRAC minutes July 2020](#).

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

- The PRAC discussed the joint assessment report issued by the Rapporteurs.
- The PRAC adopted a second list of outstanding issues (LoOI), to be addressed by the MAHs in accordance with a revised timetable ([EMA/PRAC/111338/2020\\_rev2](#)).

### 3.3. Procedures for finalisation

None

### 3.4. Re-examination procedures<sup>2</sup>

None

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<sup>1</sup> Solution, concentrate for solution

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

### 3.5. Others

None

## 4. Signals assessment and prioritisation<sup>3</sup>

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

#### 4.1.1. Immune checkpoint inhibitors:

atezolizumab – TECENTRIQ (CAP); avelumab – BAVENCIO (CAP); cemiplimab – LIBTAYO (CAP); durvalumab – IMFINZI (CAP); ipilimumab – YERVOY (CAP); pembrolizumab – KEYTRUDA (CAP); nivolumab – OPDIVO (CAP)

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

PRAC Rapporteur: Menno van der Elst

Scope: Signal of immune-mediated cystitis

EPITT 19610 – New signal

Lead Member State(s): DE, DK, NL, NO, PT

#### Background

Atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, pembrolizumab and nivolumab are immune checkpoint inhibitors (ICIs). Tecentriq, Bavencio, Libtayo, Imfinzi, Yervoy, Keytruda and Opdivo are centrally authorised medicinal products containing atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, pembrolizumab and nivolumab respectively. Tecentriq (atezolizumab) is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma and locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC), as well as in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC), whose tumours have programmed death-ligand 1 (PD-L1) expression  $\geq 1\%$  and who have not received prior chemotherapy for metastatic disease. Bavencio (avelumab) is indicated for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC) and in combination with axitinib for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC). Libtayo (cemiplimab) is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (SCC), subject to certain conditions. Imfinzi (durvalumab) is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on  $\geq 1\%$  of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. Yervoy (ipilimumab) is indicated as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma and in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma and for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. Opdivo (nivolumab) is indicated as

<sup>3</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

monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma, as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease, for the treatment of locally advanced or metastatic NSCLC and advanced renal cell carcinoma, for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL), for the treatment of recurrent or metastatic squamous cell cancer of the head and neck and for the treatment of locally advanced unresectable or metastatic urothelial carcinoma, subject to certain conditions. Keytruda (pembrolizumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma, for adjuvant treatment of adult patients with stage III melanoma and lymph node involvement who have undergone complete resection, first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a  $\geq 50\%$  tumour proportion score (TPS) or metastatic non-squamous NSCLC in adults whose tumours have no endothelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations. It is also indicated for the treatment of relapsed or refractory cHL, locally advanced or metastatic urothelial carcinoma and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a  $\geq 50\%$  TPS, subject to certain conditions.

The exposure for Tecentriq (atezolizumab) is estimated to have been more than 106,316 patients worldwide, in the period from first authorisation in 2016 to 2020. The exposure for Bavencio (avelumab) is estimated to have been more than 2,812 patient-years worldwide, in the period from first authorisation in 2017 to 2020. The exposure for Imfinzi (durvalumab) is estimated to have been more than 26,833 patient-years worldwide, in the period from first authorisation in 2017 to 2020. The exposure for Yervoy (ipilimumab) is estimated to have been more than 81,450 patients worldwide, in the period from first authorisation in 2011 to 2020. The exposure for Opdivo (nivolumab) is estimated to have been more than 429,000 patients worldwide, in the period from first authorisation in 2015 to 2019. The exposure for Keytruda (pembrolizumab) is estimated to have been more than 99,173 patient-years worldwide, in the period from first authorisation in 2015 to 2018.

During routine signal detection activities, a signal of immune-mediated cystitis was identified by France, based on 21 cases retrieved from EudraVigilance for the preferred term cystitis non-infective. The Netherlands confirmed that the signal needed initial analysis and prioritisation by the PRAC.

### **Discussion**

Having considered the available evidence from case reports in EudraVigilance, the literature and clinical trials as well as the plausible mechanism of action, the PRAC agreed that further evaluation of the signal on immune-mediated cystitis associated with ICIs is warranted.

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

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

- The MAHs for Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Yervoy (ipilimumab), Keytruda (pembrolizumab) and Opdivo (nivolumab) should submit to EMA, within 60 days, a cumulative review of the signal, including an analysis of all case reports of immune mediated/non infective cystitis and related events. A discussion on the need for amending the product information with a proposed wording should be provided.

- A 90-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

## 4.2. New signals detected from other sources

See also Annex I 14.2.

### 4.2.1. Cannabidiol – EPIDYOLEX (CAP); tacrolimus<sup>4</sup> – ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP); NAP

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Applicant(s): Astellas Pharma Europe B.V. (Advagraf, Modigraf), Chiesi Farmaceutici S.p.A. (Envarsus), GW Pharma (International) B.V. (Epidyolex), Teva B.V. (Tacforius), various

PRAC Rapporteur: Ronan Grimes

Scope: Signal of drug interaction with cannabidiol leading to tacrolimus serum level increased and toxicity

EPITT 19614 – New signal

Lead Member State(s): IE, PT, SE

#### Background

Cannabidiol is a phytocannabinoid derived from *Cannabis* species, with anticonvulsant effect and tacrolimus is a calcineurin inhibitor and potent immunosuppressant. Epidyolex (cannabidiol) is a centrally authorised product indicated, in combination with clobazam, as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), for patients 2 years of age and older. Advagraf, Envarsus and Tacforius (tacrolimus) are centrally authorised products indicated in prophylaxis of transplant rejection in adult kidney or liver allograft recipients and for treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. Modigraf (tacrolimus) is indicated in prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients and for treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.

The exposure for Epidyolex (cannabidiol) is estimated to have been more than 16,544 patient-years worldwide, in the period from first authorisation in 2018 to 2019. The exposure for Advagraf and Modigraf (tacrolimus), in the period from 2015 to 2018 is estimated to have been more than 423,986 patient-years. The exposure for Envarsus (tacrolimus) is estimated to have been more than 19,681 patients-years cumulatively in the period from the first authorisation in 2014 to 2018. Cumulated with nationally authorised medicinal products containing tacrolimus, the exposure is estimated to be above 1 million patient-years.

During routine signal detection activities, a signal of interaction between cannabidiol and systemic tacrolimus leading to tacrolimus serum level increased and toxicity was identified

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<sup>4</sup> For systemic use only

by the EMA, based on 5 cases including 4 literature cases<sup>5 6 7 8</sup>. Ireland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

## Discussion

The PRAC discussed the evidence from the literature and EudraVigilance on the cases of drug interaction with cannabidiol leading to tacrolimus serum level increased and toxicity. The PRAC noted that this interaction is currently assessed as part of a separate procedure<sup>9</sup> for Epidyolex (cannabidiol). The PRAC concurred that there is sufficient evidence to warrant the inclusion in the product information of tacrolimus<sup>10</sup>-containing medicinal products a recommendation to consider monitoring the blood levels of tacrolimus in view of the potential interaction with co-administration of cannabidiol that may lead to the increase of plasma concentrations of tacrolimus. In addition, the PRAC agreed that the current evidence is sufficient to also recommend the inclusion of the same information regarding the risk of interaction with cannabidiol, which may lead to the increase of plasma concentrations of calcineurin inhibitors and of mammalian target of rapamycin (mTOR) inhibitors, in the product information of medicinal products for systemic use containing other calcineurin inhibitor (cyclosporin) or mTOR inhibitors (everolimus, sirolimus, temsirolimus). Furthermore, the PRAC agreed that the potential interaction between tacrolimus and dronabinol or nabilone should be evaluated through an ongoing procedure for tacrolimus.

The PRAC appointed Ronan Grimes as Rapporteur for the signal.

## Summary of recommendation(s)

- The MAHs for medicinal products containing calcineurin inhibitors (tacrolimus, cyclosporin) and mTOR inhibitors (everolimus, sirolimus, temsirolimus) for systemic use should submit to the EMA or the National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update their product information once the variation procedure for Epidyolex (cannabidiol) procedure (II/0005) is concluded.

For the full PRAC recommendation, see [EMA/PRAC/570588/2020](https://www.ema.europa.eu/en/press-room/news/2020/11/2020-11-23-prac-recommendation-epidyolex) published on 23 November 2020 on the EMA website.

## 4.3. Signals follow-up and prioritisation

### 4.3.1. Anakinra - KINERET (CAP) - EMEA/H/C/000363/SDA/032; canakinumab - ILARIS (CAP) - EMEA/H/C/001109/SDA/054

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Applicant(s): Novartis Europharm Limited (Ilaris), Swedish Orphan Biovitrum AB (publ) (Kineret)

PRAC Rapporteur: Hans Christian Siersted

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<sup>5</sup> Leino A, Emoto C, Fukuda T, Privitera M, Vinks A, Alloway R. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *American Journal of Transplantation* 2019;19: 2944–2948 doi: 10.1111/ajt.15398

<sup>6</sup> DeFilippis EM, Givertz MM. Marijuana use and candidacy for heart transplantation. *The Journal of Heart and Lung Transplantation* 2019;38(6):589-92. doi: 10.1016/j.healun.2019.03.011

<sup>7</sup> Hauser N, Sahai T, Richards R, Roberts T. High on Cannabis and Calcineurin Inhibitors: A Word of Warning in an Era of Legalized Marijuana. *Case Reports in Transplantation* 2016:4028492, <https://doi.org/10.1155/2016/4028492> [accessed September 2020]

<sup>8</sup> Moadel D, Chism K. Medical Marijuana-Induced Tacrolimus Toxicity. *Psychosomatics*. 2019;60(6):603-605. doi: 10.1016/j.psych.2019.01.009

<sup>9</sup> Variation II/0005: extension of indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 1 year of age and older

<sup>10</sup> For systemic use only



Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 19566 – Follow-up to July 2020

### **Background**

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

The MAHs replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

### **Discussion**

Based on the available evidence arising from the publication by *Saper et al.* 2019<sup>11</sup> and on the cumulative reviews provided by the MAHs which suggest a possible association between anakinra/canakinumab and DRESS, the PRAC concurred that further information is necessary before a conclusion can be drawn.

The PRAC agreed on a further list of questions (LoQ) to request additional clarifications to the authors *Saper et al.* Furthermore, the PRAC agreed to request additional information from the MAHs.

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

- The authors of the publication *Saper et al.* 2019 are invited to submit to EMA, within 60 days, responses to the LoQ agreed by the PRAC.
- The MAHs for Kineret (anakinra) and Ilaris (canakinumab) should submit to EMA, within 60 days, a further analysis of all case reports with anakinra or canakinumab and DRESS, including a causality assessment and a review of the recent literature. A proposal for amending the product information and the RMP should be provided as appropriate.

#### **4.3.2. Cefepime (NAP)**

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Applicant(s): various

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Signal of drug reaction with eosinophilia and systemic symptoms (DRESS)

EPITT 17866 – Follow-up to June 2020

### **Background**

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

The MAH for the originator cefepime-containing product, Bristol-Myers Squibb, replied to the request for information on the signal of drug reaction with eosinophilia and systemic symptoms (DRESS) and the responses were assessed by the Rapporteur.

### **Discussion**

Having considered the available evidence of DRESS from the literature, EudraVigilance and the cumulative review provided by the MAH of the originator cefepime-containing product, the PRAC considered that there is insufficient evidence to establish a causal relationship

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<sup>11</sup> Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis.* 2019;78(12):1722-1731

between treatment with cefepime and DRESS. Therefore, the PRAC concluded that no further action is warranted at this stage.

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

- The MAHs of cefepime-containing product(s) should continue to monitor cases of DRESS and include a cumulative review of cases of DRESS in the next PSUR<sup>12</sup>. In addition, the MAH for the originator cefepime-containing product, Bristol-Myers Squibb, should provide a detailed discussion on new cases of DRESS within the next PSUR.

#### **4.3.3. Ceftriaxone (NAP)**

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Applicant(s): various

PRAC Rapporteur: Zane Neikena

Scope: Signal of encephalopathy

EPITT 19492 – Follow-up to April 2020

#### **Background**

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

The MAH for the originator ceftriaxone-containing product, Roche, replied to the request for information on the signal of encephalopathy and the responses were assessed by the Rapporteur.

#### **Discussion**

Having considered the available evidence from the non-clinical data, post-marketing setting, clinical trials and literature and taking into account the plausible biological mechanism, the PRAC considered that the strength of the causal relationship of encephalopathy with the use of ceftriaxone containing medicinal products is sufficient to warrant an update of the product information to reflect 'encephalopathy' as a warning and as an undesirable effect.

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

- The MAHs for ceftriaxone-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend<sup>13</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/570588/2020](#) published on 23 November 2020 on the EMA website.

#### **4.3.4. Dabrafenib - TAFINLAR (CAP) - EMEA/H/C/002604/SDA/018; trametinib - MEKINIST (CAP) - EMEA/H/C/002643/SDA/013**

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Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: David Olsen

Scope: Signal of sarcoidosis

EPITT 19574 – Follow-up to July 2020

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<sup>12</sup> Data lock point (DLP): 28/06/2021

<sup>13</sup> Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly

## Background

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

The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) replied to the request for information on the signal of sarcoidosis and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence from reported cases of sarcoidosis and the plausible potential mechanism, the PRAC agreed that the product information for dabrafenib- and trametinib-containing products should be updated to include the risk of sarcoidosis when the medicinal products are used in combination. Should more evidence become available in the future, the MAH should consider whether further updates of the product information regarding sarcoidosis are necessary when the medicinal products are used in monotherapy.

## Summary of recommendation(s)

- The MAH for Tafinlar (dabrafenib) and Mekinist (trametinib) should submit to EMA, within 60 days, a variation to amend<sup>14</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/570588/2020](#) published on 23 November 2020 on the EMA website.

### 4.3.5. [Ibrutinib - IMBRUVICA \(CAP\) - EMEA/H/C/003791/SDA/031](#)

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Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Signal of hepatitis E

EPITT 19569 – Follow-up to July 2020

## Background

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

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

## Discussion

Having considered the available evidence of cumulative review of cases of hepatitis E as well as the biological plausibility, the PRAC agreed that the product information for Imbruvica (ibrutinib) should be amended to reflect the potential risk of hepatitis E.

## Summary of recommendation(s)

- The MAH for Imbruvica (ibrutinib) should submit to the EMA, within 60 days, a variation to amend<sup>15</sup> the product information.
- In the next PSUR<sup>16</sup>, the MAH for Imbruvica (ibrutinib) should discuss whether the current risk minimisation measures (RMMs) regarding hepatotoxicity are sufficient or whether these could be improved in order to prevent serious outcomes (e.g. hepatic failure). The MAH should discuss whether a product information update is warranted in

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<sup>14</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is to be updated accordingly

<sup>15</sup> Update of section 4.4 of the SmPC. The package leaflet is to be updated accordingly

<sup>16</sup> Data lock point (DLP): 12/11/2020

order to include information on monitoring of liver function tests. The MAH should also analyse whether prolonged treatment with antiviral drugs was also reported in cases of hepatitis B and hepatitis C infections.

For the full PRAC recommendation, see [EMA/PRAC/570588/2020](#) published on 23 November 2020 on the EMA website.

4.3.6. **Immune checkpoint inhibitors:**  
atezolizumab – TECENTRIQ (CAP) – EMEA/H/C/004143/SDA/020; avelumab – BAVENCIO (CAP) – EMEA/H/C/004338/SDA/006; cemiplimab – LIBTAYO (CAP) – EMEA/H/C/004844/SDA/006; durvalumab – IMFINZI (CAP) – EMEA/H/C/004771/SDA/006; ipilimumab – YERVOY (CAP) – EMEA/H/C/002213/SDA/040; pembrolizumab – KEYTRUDA (CAP) – EMEA/H/C/003820/SDA/026; nivolumab – OPDIVO (CAP) – EMEA/H/C/003985/SDA/041

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

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Signal of eosinophilic fasciitis

EPITT 19567 – Follow-up to June 2020

#### **Background**

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

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

#### **Discussion**

Having considered the available evidence from cumulative reviews and epidemiology, the PRAC agreed that the number of cases of eosinophilic fasciitis with immune checkpoint inhibitors (ICIs) is very low and insufficient to conclude on a causal relationship between eosinophilic fasciitis and ICIs. Therefore, the PRAC concurred that no further action is warranted at this stage.

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

- The MAHs for Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Yervoy (ipilimumab), Keytruda (pembrolizumab) and Opdivo (nivolumab) should continue to monitor events of eosinophilic fasciitis as part of their routine pharmacovigilance activities.

#### 4.3.7. **Lamotrigine (NAP)**

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Applicant(s): various

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Signal of photosensitivity

EPITT 19548 – Follow-up to March 2020

## Background

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

The MAH for the originator ceftriaxone-containing product, GlaxoSmithKline B.V., replied to the request for information on the signal of photosensitivity and the responses were assessed by the Rapporteur.

## Discussion

Having considered the available evidence from the Dutch pharmacovigilance database, EudraVigilance and literature as well as the mechanism of action of lamotrigine, the PRAC agreed that there is sufficient evidence to confirm a causal relationship between lamotrigine and photosensitivity reaction.

## Summary of recommendation(s)

- The MAHs for lamotrigine-containing products should submit to relevant National Competent Authorities (NCAs) of the EU Member States, within 60 days, a variation to amend<sup>17</sup> the product information.

For the full PRAC recommendation, see [EMA/PRAC/570588/2020](#) published on 23 November 2020 on the EMA website.

## 4.4. Variation procedure(s) resulting from signal evaluation

### 4.4.1. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/II/0019

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on diverticulitis following the recommendation of signal procedure SDA/010 (EPITT 19496) adopted in May 2020. The package leaflet is updated accordingly

## Background

Baricitinib is a selective immunopressant by inhibiting (selectively and reversibly) Janus kinase (JAK)1 and JAK2. Baricitinib is indicated, as Olumiant, in monotherapy or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Olumiant (baricitinib) is also indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

Based on the evaluation of a signal procedure concluded in May 2020 on the occurrence of diverticulitis (EPITT 19496), the MAH for Olumiant (baricitinib) submitted to EMA a variation to update the product information to add the undesirable effect of diverticulitis of uncommon frequency as well as a new warning about this undesirable effect. For background information, see [PRAC minutes May 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

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<sup>17</sup> Update of sections 4.4 and 4.8 of the SmPC. The package leaflet is to be updated accordingly

### Summary of outcome(s)

- Based on the available data and the Rapporteur's assessment, the PRAC supported to update the product information<sup>18</sup> in order to add diverticulitis as a warning and as an undesirable effect with a frequency 'uncommon'.

## 5. Risk management plans (RMPs)

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

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

Please refer to the CHMP pages for upcoming information

(<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>).

See also Annex I 15.1.

#### 5.1.1. Estetrol, drospirenone - EMEA/H/C/005336

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Scope: Oral contraception

#### 5.1.2. Estetrol, drospirenone - EMEA/H/C/005382

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Scope: Oral contraception

#### 5.1.3. Lisocabtagene maraleucel - EMEA/H/C/004731, Orphan

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Applicant: Celgene Europe BV, ATMP<sup>19</sup>

Scope (accelerated assessment): Treatment of large B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B)

#### 5.1.4. Risdiplam - EMEA/H/C/005145, Orphan

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Applicant: Roche Registration GmbH

Scope (accelerated assessment): Treatment of spinal muscular atrophy (SMA)

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

See Annex I 15.2.

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

See also Annex I 15.3.

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<sup>18</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly

<sup>19</sup> Advanced therapy medicinal product

### 5.3.1. Natalizumab - TYSABRI (CAP) - EMEA/H/C/000603/X/0116

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension application to introduce a new pharmaceutical form (solution for injection), associated with a new strength (150 mg) and a new route of administration (subcutaneous use). The RMP (version 26.1) is updated accordingly

#### **Background**

Natalizumab is a monoclonal antibody selective adhesion-molecule inhibitor indicated, as Tysabri, as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis for patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The CHMP is evaluating an extension of application for Tysabri, a centrally authorised product containing natalizumab, consisting of the introduction of a new pharmaceutical form associated with a new strength and a new route of administration. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation. For further background, see [PRAC minutes July 2020](#).

#### **Summary of advice**

- The RMP for Tysabri (natalizumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 26.2 is submitted.
- The PRAC supported the recommendation to keep 'immunogenicity potential of subcutaneously administered Tysabri (anti-natalizumab antibody formation resulting in a potential adverse clinical consequence of serious hypersensitivity reactions, including anaphylaxis)' as missing information in the RMP to be further investigated under the ongoing clinical trials and post-authorisation safety studies. In addition, the PRAC agreed with the proposal to remove Tysabri (natalizumab) from the list of additional monitoring as all currently ongoing PASS are listed as category 3 studies. Finally, the PRAC advised to change the periodicity of line listings regarding progressive multifocal leukoencephalopathy (PML) cases to quarterly. Finally, the MAH should update the healthcare professional (HCP) educational material to reflect that the extended dosing interval (EDI) and the decrease in PML risk is based on intravenous (IV) data only and cannot be extrapolated to the subcutaneous (SC) injection regimen.

## **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. Alogliptin - VIPIDIA (CAP); alogliptin, metformin - VIPDOMET (CAP); alogliptin, pioglitazone - INCRESYNC (CAP) - PSUSA/00010061/202004

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Applicant(s): Takeda Pharma A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Alogliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor, metformin a biguanide and pioglitazone a thiazolidinedione. Alogliptin as Vipidia, alogliptin/metformin combination as Vipdomet and alogliptin/pioglitazone combination as Incresync, are indicated in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequately glycaemic control, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Vipidia, Vipdomet and Incresync, centrally authorised medicines containing alogliptin, alogliptin/metformin and alogliptin/pioglitazone respectively 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 Vipidia (alogliptin), Vipdomet (alogliptin/metformin) and Incresync (alogliptin/pioglitazone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on bullous pemphigoid and to add bullous pemphigoid and interstitial nephritis as undesirable effects with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>20</sup>.
- In the next PSUR, the MAH should perform a detailed review of cases of severe cutaneous adverse reactions (SCARs).

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. Canagliflozin - INVOKANA (CAP); canagliflozin, metformin - VOKANAMET (CAP) - PSUSA/00010077/202003

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Applicant(s): Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### **Background**

Canagliflozin is an inhibitor of sodium-glucose transport protein 2 (SGLT2) and metformin a biguanide. Canagliflozin is indicated, as Invokana, for the treatment of adults with

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<sup>20</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



insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate due to intolerance or contraindications and in addition to other medicinal products for the treatment of diabetes. Canagliflozin/metformin combination is indicated, as Vokanamet, for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise in patients insufficiently controlled on their maximally tolerated doses of metformin alone, in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products and in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Invokana and Vokanamet, centrally authorised medicines containing canagliflozin and canagliflozin/metformin respectively 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 Invokana (canagliflozin) and Vokanamet (canagliflozin/metformin) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on urinary tract infections (UTI) and to amend the existing information under undesirable effects on post-marketing cases of complicated UTI reported in patients treated with canagliflozin frequently leading to treatment interruption. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>21</sup>.
- The MAH should submit to EMA, within 60 days, a detailed review of cases of pancreatitis with a positive dechallenge and those with a fatal outcome together with an updated assessment. A proposal to update the product information should be provided as warranted.

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.

### **6.1.3. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/202003**

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Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

#### **Background**

Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody indicated, as Dupixent, for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy, in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of

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<sup>21</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

exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment. It is also indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Dupixent, a centrally authorised medicine containing dupilumab 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 Dupixent (dupilumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include keratitis and ulcerative keratitis as a warning and as an undesirable effect with a frequency 'uncommon' in the atopic dermatitis indication and a frequency 'rare' in the asthma indication. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>22</sup>.
- In the next PSUR, the MAH should provide further cumulative reviews of inflammatory arthritis and enthesitis, and of Stevens-Johnson syndrome (SJS). In addition, the MAH should provide an updated cumulative review and discussion on the signal of lupus erythematosus/lupus-like syndrome.

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

#### **6.1.4. Exenatide - BYDUREON (CAP); BYETTA (CAP) - PSUSA/00009147/202003**

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

### **Background**

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated, as Bydureon and Byetta, for the treatment of type 2 diabetes mellitus (T2DM) in combination with other glucose-lowering medicinal products including basal insulin in adults who have not achieved adequate glycaemic control, under certain conditions.

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

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

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<sup>22</sup> Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Bydureon and Byetta (exenatide) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include delayed gastric emptying as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>23</sup>.
- In the next PSUR, the MAH should continue to monitor cases of medication/administration errors and the outcome of the updated instructions for use (IFU) by presenting the data separately for the exenatide once weekly (QW) single dose tray (SDT), dual chamber pen (DCP) and the auto-injector. The MAH should also include a discussion on the need for further update of the IFU as needed.

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. Ipilimumab - YERVOY (CAP) - PSUSA/00009200/202003

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor indicated, as Yervoy, as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older. It is also indicated in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in adults, and in combination with nivolumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yervoy, a centrally authorised medicine containing ipilimumab 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 Yervoy (ipilimumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include solid organ transplant rejection as a warning and as an undesirable effect with a frequency 'not known'. In addition, the existing warning on haemophagocytic lymphohistiocytosis (HLH) should be amended and added as an undesirable effect with a frequency 'not known' when ipilimumab is administered in monotherapy or in combination with a programmed cell death protein 1 (PD-1) inhibitor or a programmed death-ligand 1 (PD-L1) inhibitor. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>24</sup>.

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<sup>23</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>24</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

- In the next PSUR, the MAH should provide cumulative reviews of cases of pneumonia, interstitial lung disease (ILD), rhabdomyolysis, diabetes mellitus and diabetic ketoacidosis and discuss whether a product information update is warranted.

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

#### 6.1.6. Nintedanib<sup>25</sup> - OFEV (CAP) - PSUSA/00010319/202004

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

##### **Background**

Nintedanib is a tyrosine kinase inhibitor indicated, as Ofev, for the treatment of idiopathic pulmonary fibrosis (IPF) and chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

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

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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ofev (nintedanib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of ischaemic colitis. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>26</sup>.
- In the next PSUR, the MAH should provide a detailed analysis of data from clinical trials as well as post-marketing cases of renal thrombotic microangiopathy (TMA).

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

#### 6.1.7. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/202003

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

##### **Background**

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD<sup>27</sup>20-expressing B cells indicated, as Ocrevus, for the treatment of adult patients with

<sup>25</sup> Respiratory indication(s) only

<sup>26</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

<sup>27</sup> Cluster of differentiation

relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. It is also indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ocrevus, a centrally authorised medicine containing ocrelizumab 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 Ocrevus (ocrelizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include late onset of neutropenia as a warning and as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>28</sup>.
- In the next PSUR, the MAH should provide a comparison of the frequency/reporting rate of aseptic meningitis in the multiple sclerosis (MS) population.
- The MAH should submit to the EMA, within 60 days, a variation to include the occurrence of a de-novo progressive multifocal leukoencephalopathy (PML) case following ocrelizumab treatment in the product information.

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

#### **6.1.8. Siponimod - MAYZENT (CAP) - PSUSA/00010818/202003 (with RMP)**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Evaluation of a PSUSA procedure

#### **Background**

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator indicated, as Mayzent, for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mayzent, a centrally authorised medicine containing siponimod 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 Mayzent (siponimod) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on cutaneous neoplasms with new information on the increased number of cases with long-term exposure to siponimod. In addition, basal cell carcinoma should be added as

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<sup>28</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

an undesirable effect with a frequency 'common'. The physician's checklist and the patient/caregiver guide should be updated accordingly. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>29</sup>.

- In the next PSUR, the MAH should provide detailed reviews of cases of depression and suicide/self-injury, and of urinary tract infections. A discussion on the need to update the product information should be provided as warranted. In addition, the MAH should provide a detailed description of cases of medication error.

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

#### 6.1.9. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/202003

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

##### **Background**

Velmanase alfa is a recombinant form of human alpha-mannosidase indicated, as Lamzede, as an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lamzede, a centrally authorised medicine containing velmanase alfa 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 Lamzede (velmanase alfa) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide a discussion on the need for a product information update and for additional risk minimisation measures to ensure a safe administration in a home-setting. In addition, the MAH should provide a root cause analysis of medication errors including the setting where they occurred and discuss the effectiveness of routine risk minimisation measures (instructions for reconstitution and administration).

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.

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<sup>29</sup> Update of SmPC sections 4.4, 4.8 and Annex II. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

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

### 6.2.1. Enoxaparin - INHIXA (CAP); NAP - PSUSA/00010833/202004

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Applicant(s): Techdow Pharma Netherlands B.V. (Inhixa), various

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### Background

Enoxaparin is a low molecular weight heparin (LMWH), an anti-thrombotic agent, indicated for the prophylaxis treatment of venous thromboembolic disease and the prevention of thrombus formation in extra corporeal circulation during haemodialysis as well as for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and acute coronary syndrome, under certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Inhixa, a centrally authorised medicine containing enoxaparin, and nationally authorised medicine(s) containing enoxaparin 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 enoxaparin-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, all MAHs should include a detailed review of cases of acute generalised exanthematous pustulosis (AGEP).

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

### 6.2.2. Tenofovir disoproxil - TENOFOVIR DISOPROXIL MYLAN (CAP); TENOFOVIR DISOPROXIL ZENTIVA (CAP); VIREAD (CAP); NAP - PSUSA/00002892/202003

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Applicant(s): Gilead Sciences Ireland UC (Viread), Mylan S.A.S (Tenofovir disoproxil Mylan), Zentiva k.s. (Tenofovir disoproxil Zentiva), various

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

#### Background

Tenofovir disoproxil is a nucleoside monophosphate (nucleotide) analogue indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral medicinal products and for the treatment of chronic hepatitis B (CHB), subject to certain conditions.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Tenofovir Disoproxil Mylan, Tenofovir Disoproxil Zentiva and Viread, centrally authorised medicine(s) containing tenofovir disoproxil, and nationally authorised medicine(s) containing tenofovir disoproxil 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 tenofovir disoproxil-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on bone effects and the information regarding breastfeeding for medicinal products indicated in treatment of hepatitis B virus (HBV) infections. Therefore, the current terms of the marketing authorisations should be varied<sup>30</sup>.
- In the next PSUR, the MAHs should provide detailed information on cases of osteoporosis/osteopenia reported in subjects <35 years old, together with a causality assessment.
- The MAH for Viread (tenofovir disoproxil) should submit to EMA, within 365 days, a detailed analysis of cases of neural tube defects, including information on concomitant treatment.

Additionally, the PRAC considered that the information on bone effects as amended should be implemented in the product information of other medicinal products containing tenofovir in combination, unless the wording is already in place. Further consideration should be given at the level of CHMP and CMDh.

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

### **6.2.3. Zonisamide - ZONEGRAN (CAP); NAP - PSUSA/00003152/202003**

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Applicant(s): Eisai GmbH, various

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

#### **Background**

Zonisamide is an antiepileptic benzisoxazole derivative indicated for the treatment of partial seizures, with or without secondary generalisation, subject to certain conditions.

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

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<sup>30</sup> Update of SmPC sections 4.4 and 4.6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion



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

- Based on the review of the data on safety and efficacy, the benefit-risk balance of zonisamide-containing medicinal products in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of hyperammonaemia in the existing warning on metabolic acidosis. Therefore, the current terms of the marketing authorisations should be varied<sup>31</sup>.

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

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

See also Annex I 16.3.

### **6.3.1. Ethosuximide (NAP) - PSUSA/00001316/202003**

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **Background**

Ethosuximide is a succinimide-type anticonvulsant indicated for the treatment of absence epilepsy (petit mal) in adults and children, in monotherapy or in combination with other anticonvulsants, when other forms of epilepsy coexist with absence epilepsy.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing ethosuximide 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 ethosuximide-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include thrombocytopenia and drug reaction with eosinophilia and systemic symptoms (DRESS) as undesirable effects with a frequency 'not known' and a warning on DRESS should be added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>32</sup>.
- In the next PSUR, the MAHs should provide cumulative reviews of cases of abnormal liver function and of cases of extrapyramidal undesirable effects with a proposal for updating the product information, as appropriate. In addition, the MAHs should include

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<sup>31</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

<sup>32</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

'Stevens-Johnson syndrome' and 'DRESS' as important identified risks and 'toxic epidermal necrolysis' as an important potential risk in the list of PSUR safety concerns.

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

### 6.3.2. Flucloxacillin (NAP) - PSUSA/00001402/202003

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Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### **Background**

Flucloxacillin is a beta-lactam antibiotic indicated for the treatment of infections due to sensitive Gram-positive organisms, including  $\beta$ -lactamase producing staphylococci and streptococci, such as skin and soft tissue infections, respiratory tract infections and other infections caused by flucloxacillin-sensitive organisms. It is also indicated for use as a prophylactic agent during major surgical procedures when appropriate.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing flucloxacillin 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 flucloxacillin-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include hypokalaemia as a warning and as an undesirable effect with a frequency 'not known'. In addition, for oral formulations of flucloxacillin-containing medicinal products, oesophageal pain and related events should be added as an undesirable effect with a frequency 'not known' and information on the quantity of water that should be ingested should be included. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>33</sup>.
- In the next PSUR, the MAHs should carefully monitor the safety topics of cardiac disorders, abdominal pain and upper abdominal pain, dyspepsia, chromaturia and headache with a proposal for updating the product information, as appropriate. The MAHs should also provide a cumulative review of cases of acute interstitial nephritis with a causality assessment. Based on the article by *Muilwijk et al*<sup>34</sup>, the MAHs should provide a discussion on all available information regarding the interaction between flucloxacillin and voriconazole with a proposal for updating the product information, as appropriate. In addition, based on the article by *Gellatly et al*<sup>35</sup>, the MAHs should

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<sup>33</sup> Update of SmPC sections 4.4 and 4.8 for all formulations of flucloxacillin-containing medicinal products, and sections 4.2 and 4.8 for oral formulations of flucloxacillin-containing medicinal products. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>34</sup> Muilwijk EW et al. Flucloxacillin results in suboptimal plasma voriconazole concentrations. *Antimicrob Agents Chemother.* 2017 Aug 24;61(9). pii: e00915-17. doi: 10.1128/AAC.00915-17

<sup>35</sup> Gellatly RM, Yoo S, Bergin P and Leet A. Case series of immunosuppressant drug interactions with flucloxacillin in heart transplant recipients. *Journal of Pharmacy Practice and Research.* 2019; 49: 466-70

provide a discussion on all available information regarding the interaction between flucloxacillin and the immunosuppressant drugs tacrolimus and everolimus with a proposal for updating the product information, as appropriate. Of note, the potential to rejection of heart transplants should be taken into account.

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

### 6.3.3. Fluconazole (NAP) - PSUSA/00001404/202003

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Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

#### **Background**

Fluconazole is an antifungal agent indicated for the treatment of cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, prevention of fungal infections in patients with malignancy, and deep endemic mycoses in immunocompetent patients.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing fluconazole 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 fluconazole-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include drug reaction with eosinophilia and systemic symptoms (DRESS) as a warning and as an undesirable effect with a frequency 'not known'. In addition, a warning on the risk of increased resistance due to a rise in less susceptible *Candida* species should be added. Furthermore, information on reports of congenital malformations with low-dose fluconazole use during the first trimester of pregnancy should be added. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>36</sup>.
- In the next PSUR, the MAHs should provide a cumulative review of cases of pregnancy outcomes, including in the literature, with a cumulative dose of fluconazole >150 mg anytime during pregnancy with a proposal for updating the product information, as appropriate.

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

### 6.3.4. Galantamine (NAP) - PSUSA/00001512/202003

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Applicant(s): various

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<sup>36</sup> Update of SmPC sections 4.4, 4.6, 4.8 and 5.1. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

### **Background**

Galantamine is an acetylcholinesterase inhibitor indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing galantamine 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 galantamine-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to amend the existing warning on cardiac disorders to include information on QTc prolongation/Torsade de pointes. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>37</sup>.
- In the next PSUR, the MAH should provide a detailed cumulative review of cases of QTc prolongation/Torsade de pointes with a proposal for further updating the product information, as appropriate. The MAH should also provide a follow-up discussion on the risk of hypersensitivity/anaphylactic shock.

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

## **6.3.5. Hydroxyethyl starch (HES) (NAP) - PSUSA/00001694/202003**

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Applicant(s): various

PRAC Lead: Martin Huber

Scope: Evaluation of a PSUSA procedure

### **Background**

Hydroxyethyl starch (HES) is a synthetic colloid indicated for intravenous use for infusion for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

In the context of the ongoing assessment of the submitted PSUR(s), the PRAC discussed the list of participants (LoP) for the upcoming ad-hoc expert group (AHEG) meeting.

### **Summary of conclusion(s)**

- The PRAC endorsed the LoP for the AHEG meeting on 11 November 2020.
- The PRAC recommendation is due at the December 2020<sup>38</sup> PRAC meeting.

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<sup>37</sup> Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

<sup>38</sup> Scheduled on 23-26 November 2020

### 6.3.6. Lanthanum (NAP) - PSUSA/00003175/202003

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Applicant(s): various

PRAC Lead: Roxana Stefania Stroe

Scope: Evaluation of a PSUSA procedure

#### **Background**

Lanthanum is a phosphate binding agent indicated for the control of hyperphosphatemia in chronic renal failure patients on dialysis and in adult patients with chronic kidney disease not on dialysis with serum phosphate levels  $\geq 1.78$  mmol/L ( $\geq 5.5$  mg/dL) in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing lanthanum 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 lanthanum-containing medicinal product(s) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should provide an analysis and a detailed discussion on the significant difference observed regarding the distribution of fatal cases by pharmaceutical form, cumulatively and in the reporting interval, and an assessment on the benefit-risk balance of lanthanum carbonate for each formulation. The MAH should also provide a cumulative review of cases of lanthanum deposition in human tissues with a detailed analysis of the long-term clinical effects, from all sources available including literature, with a proposal for updating the product information and additional risk minimisation measure, as appropriate.

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

### 6.3.7. Metamizole (NAP) - PSUSA/00001997/202003

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Applicant(s): various

PRAC Lead: Melinda Palfi

Scope: Evaluation of a PSUSA procedure

#### **Background**

Metamizole is a non-opioid pyrazolone derivative indicated, from 3 months of age in patients weighing at least 5 kg, for the treatment of severe or resistant pain including colicky pain, tumour pain, post-operative or post-traumatic pain, dysmenorrhoea, gingivitis, headache, toothache, pains due to infection, pneumonia and rheumatic conditions and in treatment of high fever not responding to general therapeutic measures.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing metamizole 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 metamizole-containing medicinal product(s) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include drug-induced liver injury (DILI) as an undesirable effect with a frequency 'not known'. Further to this, a warning should be included on the importance of early recognition of this undesirable effect and to avoid inadvertent re-exposure. In addition, the existing warning on pharmacokinetic interaction with bupropion and cyclosporine should be extended to include the interaction between metamizole and relevant CYP2B6<sup>39</sup> and CYP3A4<sup>40</sup> substrates. Therefore, the current terms of the marketing authorisation(s) should be varied<sup>41</sup>.
- The PRAC agreed on the content of a direct healthcare professional communication (DHPC) along with a communication plan for its distribution on the risk of DILI. The dissemination of the DHPC is to be decided at the national level, as appropriate.
- In the next PSUR, the MAH should continue to closely monitor cases of drug reaction with eosinophilia and systemic symptoms (DRESS).

Additionally, the PRAC considered that information on the risk of DILI is relevant for other fixed-drug combination products containing metamizole. The PRAC agreed that the product information of these products should be updated accordingly. Further consideration should be given at the level of CMDh.

The PRAC also agreed that the pharmacokinetic drug interaction between metamizole and CYP2B6 and/or CYP3A4 substrates resulting in potentially decreased therapeutic levels of such medicinal products and lack of efficacy should also be included in the product information of fixed-drug combination products containing metamizole, as well as in the product information of interacting medicinal products (i.e. tacrolimus, sertraline, valproate, and methadone, as well as the sensitive CYP2B6 substrate efavirenz). Further consideration should be given at the level of CHMP and CMDh.

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

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

See Annex I 16.4.

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<sup>39</sup> Cytochrome P450 2B6

<sup>40</sup> Cytochrome P450 3A4

<sup>41</sup> Update of SmPC sections 4.4, 4.5 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CMDh for adoption of a position

## 6.5. Variation procedure(s) resulting from PSUSA evaluation

### 6.5.1. Ixazomib - NINLARO (CAP) - EMEA/H/C/003844/II/0022, Orphan

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Annika Folin

Scope: Update of section 4.8 to add acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumour lysis syndrome as requested in the conclusions of the latest periodic safety update report single assessment (PSUSA) procedure (PSUSA/00010535/201911) adopted in June 2020. The package leaflet is updated accordingly

#### Background

Ixazomib is an oral proteasome inhibitor indicated, as Ninlaro, in combination with lenalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH to submit a variation to update the product information in line with the conclusions of the PSUR single assessment. For background information, see [PRAC minutes June 2020](#). The PRAC is responsible for adopting an outcome based on the assessment report from the PRAC Rapporteur, to be further considered at the level of the CHMP, responsible for adopting an opinion on this variation.

#### Summary of recommendation(s)

- Based on the available data and the Rapporteur's assessment, the PRAC agreed to update the product information<sup>42</sup> to include the undesirable effects of 'tumour lysis syndrome', 'posterior reversible encephalopathy disorders', 'transverse myelitis', 'Stevens-Johnson syndrome' and 'acute febrile neutrophilic dermatosis' with a frequency 'rare' in the tabulated summary of adverse reactions in patients treated with ixazomib in combination with lenalidomide and dexamethasone (all grades, grade 3 and grade 4). A clarification is also added on the actual undesirable effect data sources.

## 6.6. Expedited summary safety reviews<sup>43</sup>

### 6.6.1. Remdesivir - VEKLURY (CAP) - EMEA/H/C/005622/MEA 017.3

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Eva Jirsová

Scope: Sixth expedited monthly summary safety report for remdesivir for October 2020 including spontaneously reported data and data from compassionate use and expanded access programmes for the duration of the coronavirus disease (COVID-19) pandemic

#### Background

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<sup>42</sup> Update of SmPC sections 4.8. The package leaflet is to be updated accordingly

<sup>43</sup> Requirement to the compassionate use opinion to submit expedited summary safety reports for review accompanied by a summary of remdesivir distribution, in addition to the 6-monthly or annual PSURs falling within the pandemic period

Remdesivir is an antiviral medicine indicated as Veklury for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents from 12 years of age and weighing at least 40 kilograms with pneumonia requiring supplemental oxygen.

The PRAC assessed the sixth expedited summary safety report for Veklury (remdesivir) for the safety monitoring of remdesivir.

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

- The PRAC agreed that the data presented in the summary safety report are consistent with the known safety profile of remdesivir, and no new signal was identified based on the assessed data<sup>44</sup>.
- The MAH should provide, in the next pandemic report, or in the first PSUR, follow-up information of reported cases where needed. In addition, more information is requested on adverse events of special interest (AESI) including the assessment and critical discussion on causality for reported cases.
- The frequency of submission of pandemic safety reports should be changed from monthly to three-monthly.

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

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

See Annex I 17.1.

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

See Annex I 17.2.

### **7.3. Results of PASS imposed in the marketing authorisation(s)<sup>47</sup>**

None

### **7.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>48</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.

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<sup>44</sup> A separate signal procedure (EPITT 19605) on remdesivir and acute kidney injury triggered by EMA based on cumulative data from EudraVigilance is currently under evaluation

<sup>45</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>46</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>47</sup> In accordance with Article 107p-q of Directive 2001/83/EC

<sup>48</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



## **7.6. Others**

None

## **7.7. New Scientific Advice**

None

## **7.8. Ongoing Scientific Advice**

None

## **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 Annex I 18.3.

# **9. Product related pharmacovigilance inspections**

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

None

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

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

## **9.3. Others**

None

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

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

None

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

None

### **10.3. Other requests**

None

### **10.4. Scientific Advice**

None

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

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

None

### **11.2. Other requests**

None

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

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

None

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

None

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

None

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

### **12.4.1. Coronavirus (COVID-19) pandemic - update**

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The EMA secretariat updated the PRAC on the activities of the [COVID-19 EMA pandemic Task Force](#) (ETF), including an overview of ongoing clinical trials and epidemiological studies and initiatives, as well as a summary of medicines in development and medicines authorised for other indications, as potential treatments for COVID-19, and their safety surveillance. In addition, the EMA Secretariat provided the PRAC with an update on COVID-19-observational research initiatives.

### **12.4.2. Coronavirus (COVID-19) pandemic – pharmacovigilance initiatives: preparedness plan and coverage data gathering**

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The EMA Secretariat presented to PRAC on coronavirus 19 (COVID-19) vaccine pharmacovigilance initiatives including a preparedness plan and a vaccination coverage data collection. As part of the ongoing work on vaccines monitoring preparedness, the EMA is developing a document that gives an overview of the enhanced safety monitoring activities to be carried out in the EU for COVID-19 vaccines. A non-urgent information (NUI) request was distributed within the network to collect information about any existing plans or initiatives at the national levels that are currently being made for the monitoring of COVID-19 vaccines. The results were presented and PRAC discussed the next steps.

Post-meeting note: On 13 November 2020, the pharmacovigilance plan of the EU regulatory network for COVID-19 vaccines ([EMA/333964/2020](#)) was published on the EMA website together with the core requirements for RMPs of COVID-19 vaccines (see 12.14.1. ).

### **12.4.3. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group – Call for expression of interest for a PRAC representative**

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According to its mandate the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) steering group includes a number of representatives from various Committees nominated for a period of three year that may be renewed. A call for nomination of a PRAC representative to the ENCePP Steering Group for the period 2021-2023 was launched in advance of the current plenary meeting. The PRAC endorsed the nomination of Daniel Morales as the PRAC representative to the ENCePP steering group.

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

None

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

None

## **12.7. PRAC work plan**

None

## **12.8. Planning and reporting**

### **12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q3 2020 and predictions**

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The EMA Secretariat presented to the PRAC an overview of the quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes September 2020](#)<sup>49</sup>.

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

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

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None

### **12.9.2. Pharmacovigilance inspections**

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None

### **12.9.3. Pharmacovigilance audits**

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None

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

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

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None

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

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PRAC lead: Menno van der Elst, Maia Uusküla

None

### **12.10.3. PSURs repository**

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None

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

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The PRAC endorsed the draft revised EURD list, version November 2020, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of November 2020, the updated EURD list was adopted by the CHMP and CMDh at their November 2020 meetings and published on

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<sup>49</sup> Held 31 August-03 September 2020

the EMA website on 18/11/2020, see:

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

#### 12.10.5. Union reference date (EURD) list – EURD tool

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PRAC lead: Menno van der Elst

The EMA Secretariat updated PRAC on the development of the EURD tool. Following a second Member States survey on 50 EURD list entries, the EMA Secretariat worked on several iterations of the tool to improve the correlation with the selected criteria. The model developed using calibration curve from the last survey has been fine-tuned by reducing signals/EudraVigilance data to the last 3 years improving the correlation. The EMA Secretariat proposed to launch another Member States survey on 118 active substances with a data lock point (DLP) in 2025 ('parked' entries) to test the model. The PRAC supported the approach.

### 12.11. Signal management

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

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PRAC lead: Menno van der Elst

None

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

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

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None

#### 12.12.2. Additional monitoring

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None

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

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

Post-meeting note: The updated additional monitoring list was published on the EMA website on 25/11/2020, see: [Home>Human Regulatory>Post-authorisation>Pharmacovigilance>Medicines under additional monitoring>List of medicines under additional monitoring](#)

## **12.13. EudraVigilance database**

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

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None

### **12.13.2. EudraVigilance – Expert Working Group (EV-EWG) - work programme 2021-2022**

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The EMA Secretariat presented to PRAC the draft EudraVigilance Expert Working Group (EV-EWG) work programme reflecting the key activities to be performed for 2021-2022. Members were invited to send comments on the work programme and to send expression of interest to join the EV-EWG as a joint PRAC-EV EWG member by 15 November 2020. Follow-up discussion is planned in December 2020.

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

### **12.14.1. Coronavirus (COVID-19) pandemic - coreRMP19 guidance and requirements for COVID-19 vaccines**

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PRAC lead: Jean-Michel Dogné, Birgitta Grundmark, Brigitte Keller-Stanislawski, Anette Kirstine Stark, Sabine Straus, Menno van der Elst, Ulla Wändel Liminga

EMA Secretariat presented to PRAC on behalf of a drafting group composed of PRAC members and EMA staff a draft core-RMP document on requirements and guidance for COVID-19 vaccines. The PRAC adopted the document.

Post-meeting note: On 13 November 2020, the EMA published on its website 'Consideration on core requirements for RMPs of COVID19 vaccines' ([EMA/544966/2020](https://www.ema.europa.eu/en/press/news/2020/11/13/consideration-core-requirements-rmps-covid19-vaccines)).

### **12.14.2. Risk management systems**

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None

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

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None

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

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

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None

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

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None

## **12.16. Community procedures**

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

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None

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

None

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

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

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None

### **12.18.2. Safety communication**

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None

## **12.19. Continuous pharmacovigilance**

### **12.19.1. Incident management**

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None

## **12.20. Others**

### **12.20.1. Good Pharmacovigilance Practice (GVP) - update on GVP status overview – planning for 2021**

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The PRAC was provided with an overview of the GVP module status, including an update on the ongoing or planned work on new or revised GVP modules together with their scope, proposed timelines for PRAC discussion and adoption. This work should be planned for 2021 according to priorities, also taking into account current constraints as well as needs due to the Corona pandemic. The PRAC agreed with the proposal for 2021 and will be included in the PRAC work plan 2021 due for discussion in December 2020.

### **12.20.2. Strategy on measuring the impact of pharmacovigilance – PRAC interest group (IG) Impact – Revised process for prioritising impact research topics**

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PRAC lead: Antoine Pariente

As a follow-up to the September 2020 discussion (for background, see [PRAC minutes September 2020](#)<sup>50</sup>), the EMA Secretariat presented to PRAC on behalf of the PRAC interest group Impact a revised proposal for prioritising impact research topics for selected procedures, replacing the current monthly notification process. The PRAC endorsed the revised proposal. The new process will start as of January 2021.

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<sup>50</sup> Held 31 August-03 September 2020

## 13. Any other business

None

## 14. Annex I – Signals assessment and prioritisation<sup>51</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>52</sup>.

### 14.2. New signals detected from other sources

#### 14.2.1. Trastuzumab emtansine – KADCYLA (CAP)

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Applicant(s): Roche Registration GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Signal of extravasation and epidermal necrosis

EPITT 19611 – New signal

Lead Member State(s): DK

## 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. Adalimumab - EMEA/H/C/005188

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Scope: Treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis and paediatric uveitis

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<sup>51</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>52</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



### 15.1.2. Bevacizumab - EMEA/H/C/005640

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Scope: Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer and metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer and persistent, recurrent, or metastatic carcinoma of the cervix. First-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer. First line treatment of patients with advanced and/or metastatic renal cell cancer

## 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. Agomelatine - THYMANAX (CAP) - EMEA/H/C/000916/WS1849/0045; VALDOXAN (CAP) - EMEA/H/C/000915/WS1849/0047

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

PRAC Rapporteur: Pernille Harg

Scope: Submission of an updated RMP (version 23.1) in order to revise the list of safety concerns, important identified and potential risks in line with revision 2 of GVP module V on 'Risk management systems'. In addition, the completed studies have been deleted and, as agreed in the conclusions of LEG 031 adopted in January 2019, the frequency of the educational material distribution is updated to once yearly

### 15.2.2. Histamine dihydrochloride - CEPLENE (CAP) - EMEA/H/C/000796/II/0040

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Applicant: Noventia Pharma S.r.l.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Submission of an updated RMP (version 8.1) in order to include information about the termination/finalisation of: 1) non-interventional study Ceplene-3290 (listed as a category 3 study in the RMP): an open study designed to gain further knowledge on Ceplene (histamine dihydrochloride) under day to day conditions with special emphasis on tolerability, practicability, usage, and measurable minimal residual disease and course of blast cells and; 2) post-authorisation efficacy study (PAES) Ceplene cohort study 3306: an international, multicentre, observational, non-interventional, registry-based cohort study aiming to describe and evaluate minimal residual disease (MRD) at baseline and follow-up for the assessment of the anti-leukaemic activity of Ceplene (histamine dihydrochloride)/interleukin-2 (IL-2) as remission maintenance therapy in adult patients with acute myeloid leukaemia (AML) in first complete remission (CR1) compared to matched control patients who did not receive Ceplene (histamine dihydrochloride)/IL-2. In addition, the RMP is brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). As a consequence, the list of safety concerns is amended in particular 'drug effect decreased as a consequence of drug interaction' is added as a new important potential risk

### 15.2.3. Iloprost - VENTAVIS (CAP) - EMEA/H/C/000474/II/0066

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Applicant: Bayer AG

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 8.0) to introduce respiratory tract infection as an important potential risk as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure (PSUSA/00001724/201709) adopted in May 2018. In addition, the MAH took the opportunity to update the RMP in line with revision 2 of GVP module V on 'Risk management systems'

### 15.2.4. Mannitol - BRONCHITOL (CAP) - EMEA/H/C/001252/II/0042, Orphan

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Applicant: Pharmaxis Europe Limited

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of an updated RMP (version 9.0) brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template). The MAH took the opportunity to review the safety information and proposed to reclassify 'cough' from an important potential risk to an important identified risk; to remove the important identified risks of 'bronchospasm during and after the initiation dose assessment' and 'bronchospasm during long term use'; to remove the important potential risk of 'cough-related sequelae', 'off label use in non-cystic fibrosis (CF) bronchiectasis', 'off label use in paediatric/adolescent CF patients (aged 6-17 years)', 'administration of Bronchitol via the wrong inhaler device' and 'starting Bronchitol treatment without completing the full Bronchitol initiation dose assessment (BIDA) dose'; to remove the missing information of 'patients requiring home oxygen or needing assisted ventilation', 'children <6 years of age', 'pregnancy and lactation', 'risks associated with long-term use' from the list of safety concerns; to add 'increased risk of respiratory or systemic infection' as an important potential risk replacing 'pulmonary abscess on continued use', 'septicaemia on continued use', 'increased risk of bacteria sputum identified or infections with extended use of Bronchitol' and 'microbial infection via a contaminated inhaler device' previously classified as important potential risks. In addition, the pharmacovigilance plan is updated with completed studies. Finally, the RMP is updated as requested in the conclusions of the periodic safety update report single assessment (PSUSA) procedure (PSUSA/00009226/201904) adopted at the November 2019 PRAC meeting

### 15.2.5. Pramipexole - MIRAPEXIN (CAP) - EMEA/H/C/000134/WS1897/0096; SIFROL (CAP) - EMEA/H/C/000133/WS1897/0087

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of an updated RMP (version 12.0) as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00002491/201904) adopted in December 2019 in order to remove cardiac failure from the list of important identified risks and to amend the information on dopamine agonist withdrawal syndrome (DAWS) as an important identified risk

15.2.6. [Tacrolimus - ADVAGRAF \(CAP\) - EMEA/H/C/000712/WS1805/0057; MODIGRAF \(CAP\) - EMEA/H/C/000954/WS1805/0035; NAP](#)

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of an updated RMP (version 3) in order to add a non-interventional study related to the safety concerns of use during pregnancy and use during lactation. The MAH took the opportunity to combine the two important potential risks of 'exchangeability between the granule and capsule formulations of tacrolimus' for Modigraf (tacrolimus) and 'if administered accidentally either arterially or perivascularly, the reconstituted solution may cause irritation at the injection site' for Prograf (tacrolimus) concentrate for solution for infusion into the important identified risk of 'medication errors'. Finally, the RMP is updated in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.2.7. [Tolvaptan - JINARC \(CAP\) - EMEA/H/C/002788/II/0029](#)

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Applicant: Otsuka Pharmaceutical Netherlands B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Submission of an updated RMP (version 14.4) to include dehydration and the pregnancy prevention programme as additional risk minimisation measures (aRMM) in order to align the RMP with Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'

15.2.8. [Trabectedin - YONDELIS \(CAP\) - EMEA/H/C/000773/II/0061](#)

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Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of an updated RMP (version 9.0) in order to reflect new available data from completed studies, removal of safety concerns and removal of a target follow-up questionnaire. The RMP is also brought in line with revision 2.0.1 of the guidance on the format of RMP in the EU (template)

15.2.9. [Umeclidinium bromide - INCRUSE ELLIPTA \(CAP\) - EMEA/H/C/002809/WS1589/0029; ROLUFTA ELLIPTA \(CAP\) - EMEA/H/C/004654/WS1589/0014](#)

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Applicant: GlaxoSmithKline (Ireland) Limited (Incruse Ellipta), GlaxoSmithKline Trading Services Limited (Rolufta Ellipta)

PRAC Rapporteur: Ilaria Baldelli

Scope: Submission of an updated RMP (version 7.1) following completion of study WWE117397 (listed as a category 3 in the RMP): a post-authorisation safety electronic medical records database retrospective cohort study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) in the primary care setting. In addition, updates are reflected in the RMP with regard to study 201038 (listed as a category 1 in the RMP/Annex II): a post authorisation safety observational cohort study to quantify the incidence of selected cardiovascular and

cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients using inhaled UMEC/VI combination or inhaled UMEC versus tiotropium, as requested in the conclusions of procedure PSA/S/0032.3 adopted in November 2019. These include updates of the primary and secondary objectives to include the composite endpoint and the sample size for the study. Finally, the RMP is brought in line with revision 2 of GVP module V on 'Risk management systems'

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

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

#### **15.3.1. Avatrombopag - DOPTLET (CAP) - EMEA/H/C/004722/II/0004/G**

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Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Eva Segovia

Scope: Grouped variations consisting of: 1) extension of indication to include the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 5.3 of the SmPC is updated with data from juvenile toxicity studies; 2) addition of a pack size of 30 tablets with subsequent updates of sections 6.5 and 8 of the SmPC. The package leaflet, labelling and the RMP (version 2.1) are updated in accordance. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

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

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Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

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

#### **15.3.3. Belatacept - NULOJIX (CAP) - EMEA/H/C/002098/II/0070**

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Extension of indication to include the use of belatacept in conversion from a calcineurin inhibitor-based regimen to a belatacept-based regimen post transplantation. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 18.0) are updated in accordance. Furthermore, the MAH took

the opportunity to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1) and to update it with regard to sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### 15.3.4. [Carfilzomib - KYPROLIS \(CAP\) - EMEA/H/C/003790/II/0045, Orphan](#)

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Extension of existing indication to include combination of Kyprolis (carfilzomib) with daratumumab and dexamethasone. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance

#### 15.3.5. [Fluticasone furoate, umeclidinium, vilanterol - ELEBRATO ELLIPTA \(CAP\) - EMEA/H/C/004781/X/0014/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184 mcg/55 mcg/22 mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

#### 15.3.6. [Fluticasone furoate, umeclidinium, vilanterol - TEMYBRIC ELLIPTA \(CAP\) - EMEA/H/C/005254/X/0004/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184 mcg/55 mcg/22 mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

#### 15.3.7. [Fluticasone furoate, umeclidinium, vilanterol - TRELEGY ELLIPTA \(CAP\) - EMEA/H/C/004363/X/0012/G](#)

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Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Grouped application consisting of: 1) extension application to introduce a new strength (184 mcg/55 mcg/22 mcg); 2) extension of indication to add maintenance treatment in adult patients with asthma. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The package leaflet and the RMP (version 2.2) are updated in accordance

### [15.3.8. Follitropin delta - REKOVELLE \(CAP\) - EMEA/H/C/003994/II/0022](#)

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Applicant: Ferring Pharmaceuticals A/S

PRAC Rapporteur: Menno van der Elst

Scope: Update of section 4.2 of the SmPC in order to introduce a new anti-Müllerian hormone (AMH) assay to determine the dose of follitropin delta, following an agreed recommendation. The RMP (version 5.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems'. The MAH took the opportunity to amend section 4.4 of the SmPC to introduce traceability information. Finally, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

### [15.3.9. Ipilimumab - YERVOY \(CAP\) - EMEA/H/C/002213/WS1840/0084; nivolumab - OPDIVO \(CAP\) - EMEA/H/C/003985/WS1840/0089](#)

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Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Extension of indication to include treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) for combination treatment with Opdivo (nivolumab) and Yervoy (ipilimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMPs (Opdivo version 18.0, Yervoy version 29.0) are updated in accordance

### [15.3.10. Lacosamide - LACOSAMIDE ACCORD \(CAP\) - EMEA/H/C/004443/X/0007](#)

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Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Ulla Wändel Liminga

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

### [15.3.11. Lipegfilgrastim - LONQUEX \(CAP\) - EMEA/H/C/002556/II/0058/G](#)

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Applicant: Teva B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Grouped variations consisting of an extension of indication to include treatment of the paediatric population and introduction of an age appropriate presentation in vials. 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 12.0) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet. Furthermore, the product information is brought in line with the latest quality review of documents (QRD) template (version 10.1)

### [15.3.12. Nintedanib - VARGATEF \(CAP\) - EMEA/H/C/002569/II/0035/G](#)

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Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: Grouped variations consisting of: 1) update of sections 4.5, 4.6 and 5.2 of the SmPC to reflect the results of study 1199-0340 conducted in female patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) to investigate a potential interaction between nintedanib and a combined oral contraceptive (COC) containing ethinylestradiol/levonorgestrel; 2) update of sections 4.3 and 4.6 of the SmPC to introduce a new contraindication of pregnancy. This follows the update for Ofev (nintedanib) on SSc-ILD introduced in the context of variation II/0026 finalised in February 2020 and as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00010318/201910) adopted in May 2020. The package leaflet and the RMP (version 7.0) are updated accordingly

### 15.3.13. Ocrelizumab - OCREVUS (CAP) - EMEA/H/C/004043/II/0021

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of section 4.4 in order to include the term 'anaphylaxis' among the possible symptoms of infusion-related reactions (IRRs), following an analysis of cases retrieved by anaphylactic reaction MedDRA<sup>53</sup> narrow standardised MedDRA queries (SMQ). The MAH took the opportunity to update Annex II-C on 'Other conditions and requirements of the marketing authorisation' and Annex II-D on 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' 'in line with the latest quality review of documents (QRD) template (version 10.1). The RMP (version 6.0) is updated accordingly

### 15.3.14. Pegvisomant - SOMAVERT (CAP) - EMEA/H/C/000409/II/0098/G

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Adrien Inoubli

Scope: Grouped variations consisting of: 1) update of section 4.4 of the SmPC to remove the warning on growth hormone secreting tumours, consequential to the removal of pituitary tumour growth as a potential risk from the RMP. The package leaflet is updated accordingly; 2) update of the RMP (version 2.0) to reflect the evaluation of the final results of study A6291010 (ACROSTUDY) (listed as a category 3 study in the RMP): an open-label, global, multicentre, non-interventional PASS performed to monitor the long-term safety and outcomes of pegvisomant treatment in clinical practice as per the conclusions of variation II/0089 adopted in July 2019. The RMP is also brought in line with revision 2 of GVP module V on 'Risk management systems'

### 15.3.15. Rituximab - BLITZIMA (CAP) - EMEA/H/C/004723/WS1893/0034; RITEMVIA (CAP) - EMEA/H/C/004725/WS1893/0034; TRUXIMA (CAP) - EMEA/H/C/004112/WS1893/0037

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Hans Christian Siersted

Scope: Submission of the final clinical study report (CSR) for study CT-P10 3.4: a phase 3,

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<sup>53</sup> Medical Dictionary for Regulatory Activities

randomised, parallel-group, active-controlled, double-blind study to compare efficacy and safety between CT-P10 (Blitzima/Ritemvia/Truxima (biosimilar rituximab)) and Rituxan/Mabthera (rituximab) in patients with low tumour burden follicular lymphoma (LTBFL). The RMP (version 10.1) is updated accordingly

#### **15.3.16. Rivaroxaban - XARELTO (CAP) - EMEA/H/C/000944/X/0074/G**

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Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped applications consisting of: 1) extension application to introduce a new pharmaceutical form, granules for oral suspension (1 mg/mL); 2) extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto (rivaroxaban) 15 mg and 20 mg tablets. As a consequence, sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The package leaflet and the RMP (version 12.1) are updated accordingly. In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated for all other dose strengths (2.5/10 mg and 15/20 mg initiation packs). Furthermore, the MAH took the opportunity to update the product information with regard to sodium content in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### **15.3.17. Rucaparib - RUBRACA (CAP) - EMEA/H/C/004272/II/0020**

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Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to update the information on the use of rucaparib in patients with hepatic impairment based on final results from part I of study CO-338-078 (listed as a category 3 study in the RMP): a phase 1, open-label, parallel group study to determine the pharmacokinetics, safety and tolerability of rucaparib in patients with an advanced solid tumour and either moderate hepatic impairment or normal hepatic function. The package leaflet and the RMP (version 4.0) are updated accordingly. The MAH took the opportunity to introduce minor corrections in the SmPC, to update the list of local representatives in the package leaflet, and to bring the product information in line with the latest quality review of documents (QRD) template (version 10.1).and in line with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'

#### **15.3.18. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/WS1830/0032; NEPARVIS (CAP) - EMEA/H/C/004343/WS1830/0029**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Submission of the final report from study CLCZ696D2301 (PARAGON HF) (listed as a category 3 study in the RMP): a multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 (sacubitril/valsartan)



compared to valsartan, on morbidity and mortality in heart failure patients (NYHA<sup>54</sup> class II-IV) with preserved ejection fraction to evaluate cognitive function. The RMP (version 2.0) is updated accordingly

#### **15.3.19. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0026**

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Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (350 mg/mL oral solution). The RMP (version 0.1) is updated in accordance

#### **15.3.20. Sodium phenylbutyrate - PHEBURANE (CAP) - EMEA/H/C/002500/X/0028**

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Applicant: Eurocept International B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension application to introduce a new pharmaceutical form associated with a new strength (500 mg film-coated tablets). The RMP (version 0.1) is updated in accordance

#### **15.3.21. Stiripentol - DIACOMIT (CAP) - EMEA/H/C/000664/X/0032**

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Applicant: Biocodex

PRAC Rapporteur: Maia Uusküla

Scope: Extension application to add a new strength (100 mg capsules). The RMP (version 2.0) is updated in accordance

## **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. Abemaciclib - VERZENIOS (CAP) - PSUSA/00010724/202003**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

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<sup>54</sup> New York Heart Association

Scope: Evaluation of a PSUSA procedure

#### 16.1.2. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/202003

Applicant: Merck Europe B.V.

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

#### 16.1.3. Brolucizumab - BEOVU (CAP) - PSUSA/00010829/202004

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.4. Cemiplimab - LIBTAYO (CAP) - PSUSA/00010780/202003

Applicant: Regeneron Ireland Designated Activity Company (DAC)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.5. Certolizumab - CIMZIA (CAP) - PSUSA/00000624/202003

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.6. Dacomitinib - VIZIMPRO (CAP) - PSUSA/00010757/202003

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.7. Dapagliflozin - EDISTRIDE (CAP); FORXIGA (CAP) - PSUSA/00010029/202004

Applicant(s): AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.8. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/202003

Applicant: Takeda Pharma A/S, ATMP<sup>55</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

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<sup>55</sup> Advanced therapy medicinal product

Scope: Evaluation of a PSUSA procedure

#### 16.1.9. Emtricitabine - EMTRIVA (CAP) - PSUSA/00001209/202004

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.10. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - PSUSA/00010515/202004

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.11. Emtricitabine, tenofovir disoproxil - TRUVADA (CAP) - PSUSA/00001210/202004

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

#### 16.1.12. Fostamatinib - TAVLESSE (CAP) - PSUSA/00010819/202004

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.13. Galcanezumab - EMGALITY (CAP) - PSUSA/00010733/202003

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.14. Gilteritinib - XOSPATA (CAP) - PSUSA/00010832/202003

Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

#### 16.1.15. Herpes zoster vaccine (recombinant, adjuvanted) - SHINGRIX (CAP) - PSUSA/00010678/202004

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Sonja Hrabcik

Scope: Evaluation of a PSUSA procedure

#### 16.1.16. Histamine<sup>56</sup> - CEPLENE (CAP) - PSUSA/00001610/202004

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Applicant: Noventia Pharma S.r.l.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.17. Insulin glulisine - APIDRA (CAP) - PSUSA/00001752/202004

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Applicant: Sanofi-Aventis Deutschland GmbH

PRAC Rapporteur: Hans Christian Siersted

Scope: Evaluation of a PSUSA procedure

#### 16.1.18. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/202003

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

#### 16.1.19. Lorlatinib - LORVIQUA (CAP) - PSUSA/00010760/202003

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Evaluation of a PSUSA procedure

#### 16.1.20. Lusutrombopag - MULPLEO (CAP) - PSUSA/00010755/202003

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Applicant: Shionogi B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

#### 16.1.21. Meningococcal group A, C, W-135, Y conjugate vaccine (conjugated to *Corynebacterium diphtheriae* CRM<sub>197</sub> protein) - MENVEO (CAP) - PSUSA/00001969/202003

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Applicant: GSK Vaccines S.r.l

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

#### 16.1.22. Mogamulizumab - POTELIGEO (CAP) - PSUSA/00010741/202003

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Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Hans Christian Siersted

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<sup>56</sup> Indicated for the treatment of acute myeloid leukaemia (AML)

Scope: Evaluation of a PSUSA procedure

#### 16.1.23. Naldemedine - RIZMOIC (CAP) - PSUSA/00010753/202003

Applicant: Shionogi B.V.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Evaluation of a PSUSA procedure

#### 16.1.24. Niraparib - ZEJULA (CAP) - PSUSA/00010655/202003

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

#### 16.1.25. Risankizumab - SKYRIZI (CAP) - PSUSA/00010765/202003

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Evaluation of a PSUSA procedure

#### 16.1.26. Sodium zirconium cyclosilicate - LOKELMA (CAP) - PSUSA/00010675/202003

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

#### 16.1.27. Talazoparib - TALZENNA (CAP) - PSUSA/00010781/202004

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

#### 16.1.28. Trifluridine, tipiracil - LONSURF (CAP) - PSUSA/00010517/202003

Applicant: Les Laboratoires Servier

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

#### 16.1.29. Vandetanib - CAPRELSA (CAP) - PSUSA/00009327/202004

Applicant: Genzyme Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Evaluation of a PSUSA procedure

#### **16.1.30. Yttrium (<sup>90</sup>Y) chloride - YTRACIS (CAP); YTTRIGA (CAP) - PSUSA/00003137/202003**

Applicant(s): Cis Bio International (Ytracis), Eckert & Ziegler Radiopharma GmbH (Yttriga)

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

None

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

##### **16.3.1. Ascorbic acid, paracetamol, pheniramine maleate (NAP) - PSUSA/00002368/202003**

Applicant(s): various

PRAC Lead: Maia Uusküla

Scope: Evaluation of a PSUSA procedure

##### **16.3.2. Trandolapril, verapamil (NAP) - PSUSA/00003005/202003**

Applicant(s): various

PRAC Lead: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

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

##### **16.4.1. Lenalidomide - REVLIMID (CAP) - EMEA/H/C/000717/LEG 050**

Applicant: Celgene Europe BV

PRAC Rapporteur: Tiphaine Vaillant

Scope: Detailed review of cases of B-cell acute lymphoblastic leukaemia as requested in the conclusions of the PSUR single assessment (PSUSA) procedure (PSUSA/00001838/201912) adopted in July 2020

## **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>57</sup>**

### **17.1.1. Betibeglogene autotemcel – ZYNTGLO (CAP) - EMEA/H/C/PSA/S/0059**

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Applicant: Bluebird bio (Netherlands) B.V., ATMP<sup>58</sup>

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a non-interventional PASS to collect longitudinal data on clinical outcomes of patients with transfusion-dependent  $\beta$ -thalassaemia (TDT) who have received treatment with Zynteglo (betibeglogene autotemcel) in the post-marketing setting

### **17.1.2. Eliglustat – CERDELGA (CAP) - EMEA/H/C/PSA/S/0054.1**

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Applicant: Genzyme Europe BV

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to PSA/S/0054 [substantial amendment to a protocol previously agreed in December 2018 (PSA/S/0035) for a prospective multicentre observational post authorisation safety sub-registry to characterise the long-term safety profile of commercial use of Cerdelga (eliglustat) in adult patients with Gaucher disease] as per the request for supplementary information (RSI) adopted in June 2020

### **17.1.3. Methylphenidate hydrochloride (NAP) - EMEA/H/N/PSP/S/0064.5**

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

PRAC Rapporteur: Martin Huber

Scope: MAH's response to PSP/S/0064.4 [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] as per the request for supplementary information (RSI) adopted in June 2020

### **17.1.4. Parathyroid hormone – NATPAR (CAP) - EMEA/H/C/PSA/S/0053.1**

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Applicant: Shire Pharmaceuticals Ireland

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to PSA/S/0053 [substantial amendment to a protocol previously agreed in March 2018 (PSA/S/0026) for study PARADIGM (physicians advancing disease knowledge in hypoparathyroidism): a registry for subjects with chronic hypoparathyroidism to explore physicians advancing disease knowledge in hypoparathyroidism] as per the request for supplementary information (RSI) adopted in June 2020

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<sup>57</sup> In accordance with Article 107n of Directive 2001/83/EC

<sup>58</sup> Advanced therapy medicinal product

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

### **17.2.1. Darbepoetin alfa - ARANESP (CAP) - EMEA/H/C/000332/MEA 092.1**

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Applicant: Amgen Europe B.V.

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 092 [protocol for study 20190404: a retrospective cohort study to assess the use of erythropoiesis stimulating agents (ESAs) in subjects receiving myelosuppressive chemotherapy in Europe] as per the request for supplementary information (RSI) adopted in May 2020

### **17.2.2. Interferon beta-1a - AVONEX (CAP) - EMEA/H/C/000102/MEA 088.1**

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Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: MAH's response to MEA 088 [protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden] as per the request for supplementary information (RSI) adopted in April 2020

### **17.2.3. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/MEA 045.1**

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Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 045 [protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden] as per the request for supplementary information (RSI) adopted in April 2020

### **17.2.4. Interferon beta-1b - BETAFERON (CAP) - EMEA/H/C/000081/MEA 025.1**

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Applicant: Bayer AG

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 025 [protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden] as per the request for supplementary information (RSI) adopted in April 2020

### **17.2.5. Interferon beta-1b - EXTAVIA (CAP) - EMEA/H/C/000933/MEA 023.1**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 023 [protocol for a joint PASS for study 2600153 (INFORM):

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<sup>59</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



an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden] as per the request for supplementary information (RSI) adopted in April 2020

#### 17.2.6. Luspatercept - REBLOZYL (CAP) - EMEA/H/C/004444/MEA 004

Applicant: Celgene Europe BV

PRAC Rapporteur: Laurence de Fays

Scope: Amendment to a protocol previously agreed in the framework of the initial marketing authorisation application (MAA) procedure for study ACE-536-LTFU-001: a phase 3b, open label, single-arm rollover study to evaluate long term safety in subjects who have participated in other luspatercept clinical trials in order to amend the iron parameters

#### 17.2.7. Peginterferon beta-1a - PLEGRIDY (CAP) - EMEA/H/C/002827/MEA 010.1

Applicant: Biogen Netherlands B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: MAH's response to MEA 010 [protocol for a joint PASS for study 2600153 (INFORM): an observational study regarding interferon beta exposure in the second and third trimesters of pregnancy - a register-based drug utilisation study (DUS) in Finland and Sweden] as per the request for supplementary information (RSI) adopted in April 2020

#### 17.2.8. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/MEA 002.1

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Substantial amendment to a protocol previously agreed in September 2018 (MEA 002) for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final study report expected 5 years after start of study]

#### 17.2.9. Semaglutide - RYBELSUS (CAP) - EMEA/H/C/004953/MEA 002

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Substantial amendment to a protocol previously agreed in September 2018 (Ozempic MEA 002) for study NN9535-4447: an epidemiological database study to estimate the risk of pancreatic cancer in patients with type 2 diabetes mellitus (T2DM) taking semaglutide - a cohort study based on Nordic registry data [final study report expected 5 years after start of study]

#### 17.2.10. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/MEA 015.1

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: MAH's response to MEA 015 [protocol for study A3921334: a non-interventional PASS to evaluate the effectiveness of additional risk minimisation measures (aRMM) materials for Xeljanz (tofacitinib) in Europe via a survey of healthcare professionals (HCPs), as requested in the conclusions of the referral procedure under Article 20 of Regulation (EC) No 726/2004 (EMA/H/A-20/1485) finalised in November 2019] as per the request for supplementary information (RSI) adopted in July 2020

### **17.3. Results of PASS imposed in the marketing authorisation(s)<sup>60</sup>**

None

### **17.4. Results of PASS non-imposed in the marketing authorisation(s)<sup>61</sup>**

#### **17.4.1. Acridinium - BRETARIS GENUAIR (CAP) - EMA/H/C/002706/WS1795/0043; EKLIRA GENUAIR (CAP) - EMA/H/C/002211/WS1795/0043**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study D6570R00002 (listed as a category 3 study in the RMP): a descriptive, non-interventional, multinational European cohort study of new users of acridinium, acridinium/formoterol, and other selected chronic obstructive pulmonary disease (COPD) medications to describe the characteristics and patterns of use. As a consequence, the following safety concerns listed as missing information in the RMP are removed: 'safety in patients with hepatic or severe renal impairment', 'safety in patients with benign hyperplasia or urinary retention' and 'use in pregnancy or lactation'. The RMP (version 8.0) is updated accordingly

#### **17.4.2. Acridinium, formoterol fumarate dihydrate - BRIMICA GENUAIR (CAP) - EMA/H/C/003969/WS1794/0029; DUAKLIR GENUAIR (CAP) - EMA/H/C/003745/WS1794/0029**

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Applicant: AstraZeneca AB

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study D6570R00002 (listed as a category 3 study in the RMP): a descriptive, non-interventional, multinational European cohort study of new users of acridinium, acridinium/formoterol, and other selected chronic obstructive pulmonary disease (COPD) medications to describe the characteristics and patterns of use. As a consequence, the following safety concerns listed as missing information in the RMP are removed 'safety in patients with hepatic or severe renal impairment', 'safety in patients with benign hyperplasia or urinary retention' and 'use in pregnancy or lactation'. The RMP (version 5.0) is updated accordingly

#### **17.4.3. Baricitinib - OLUMIANT (CAP) - EMA/H/C/004085/II/0017**

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Applicant: Eli Lilly Nederland B.V.

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

<sup>61</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

PRAC Rapporteur: Adam Przybylkowski

Scope: Submission of the final report from study I4V-MC-B010 (listed as a category 3 study in the RMP): an observational, multinational cross-sectional survey amongst rheumatologists to assess the effectiveness of the risk minimisation measures (RMM) for Olumiant (baricitinib). The RMP (version 9.2) is updated accordingly. The MAH took the opportunity to remove from the RMP three safety concerns listed as missing information namely 'use in combination with biologic disease-modifying anti-rheumatic drugs (bDMARDs) or with other Janus kinase (JAK) inhibitors', 'use in patients with severe hepatic impairment', 'effect on fertility, on pregnancy and the foetus', and 'use in breastfeeding' as requested in the conclusions of variation II/006 finalised in July 2018

#### **17.4.4. Everolimus - AFINITOR (CAP) - EMEA/H/C/001038/WS1923/0068; VOTUBIA (CAP) - EMEA/H/C/002311/WS1923/0067**

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Martin Huber

Scope: Submission of the final clinical study report (CSR) for study CRAD001MIC03 (TOSCA): an international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex (TSC). The RMP (version 15.0) is updated accordingly and in line with the conclusions of variation WS1671 adopted in October 2019

#### **17.4.5. Ledipasvir, sofosbuvir - HARVONI (CAP) - EMEA/H/C/003850/WS1915/0091; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1915/0051; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS1915/0043**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Submission of the final report from study GS-US-248-0123 (listed as a category 3 study in the RMP): a long-term observational follow-up registry of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection. The RMPs (Harvoni version 7.1, Eplclusa version 6.1, Vosevi version 3.1) are updated accordingly

#### **17.4.6. Mirabegron - BETMIGA (CAP) - EMEA/H/C/002388/II/0033**

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Applicant: Astellas Pharma Europe B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final study report for study 178-CL-114: an evaluation of cardiovascular events in users of mirabegron and other treatments for overactive bladder

#### **17.4.7. Teriparatide - FORSTEO (CAP) - EMEA/H/C/000425/II/0054**

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Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of the final report for the European Union (EU) component of study B3D-MC-GHBX(2.1): a registry to estimate the incidence of osteosarcoma in patients who have received treatment with Forteo (teriparatide)

#### **17.4.8. Tofacitinib - XELJANZ (CAP) - EMEA/H/C/004214/II/0023**

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Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from study A3921205 (listed as a category 3 study in the RMP): an observational PASS within the Consortium of Rheumatology Researchers of North America (CORRONA) registry comparing rates of malignancy, cardiovascular and serious infection outcomes among patients treated for moderately to severely active rheumatoid arthritis. The RMP (version 10.1) is updated accordingly

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

#### **17.5.1. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 003**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report of the safety surveillance programme using the Register for Antirheumatic Therapies in Sweden (ARTIS): a national prospective, observational, uncontrolled cohort study to evaluate the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and other rheumatic disease patients treated with adalimumab

#### **17.5.2. Adalimumab - IMRALDI (CAP) - EMEA/H/C/004279/MEA 004**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual registry report of the safety surveillance programme using the Spanish Registry for Adverse Events for Biological Therapy in Rheumatic Diseases (BIOBASASER)

#### **17.5.3. Belimumab - BENLYSTA (CAP) - EMEA/H/C/002015/MEA 003.4**

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Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of a biennial report for study BEL115467/HGS1006-C1113: a randomized, double-blind placebo-controlled large safety study, based on a protocol agreed with CHMP, evaluating over a minimum of one year the incidence of all-cause mortality and adverse events of special interest (AESI) in patients with systemic lupus erythematosus receiving belimumab

#### 17.5.4. Damoctocog alfa pegol - JIVI (CAP) - EMEA/H/C/004054/MEA 003.1

Applicant: Bayer AG

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003 [tenth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149 (listed as a category 3 study in the RMP): evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry [final clinical study report (CSR) expected in December 2021]] as per the request for supplementary information (RSI) adopted in May 2020

#### 17.5.5. Dimethyl fumarate - SKILARENCE (CAP) - EMEA/H/C/002157/MEA 001.4

Applicant: Almirall S.A

PRAC Rapporteur: Annika Folin

Scope: Second annual interim results for study M-41008-40 (listed as a category 3 study in the RMP): an observational PASS in European psoriasis registers to evaluate the long-term safety of Skilarence (dimethyl fumarate) used for the treatment of patients with moderate to severe psoriasis [future due date(s): end of data collection: Q1 2027; final study report expected within a year of availability of the final data set]

#### 17.5.6. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 007.5

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Fifth annual report for study CNTO148ART4001: a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers; together with the study summary results for the 2020 interval report for study CNTO148ART4001

#### 17.5.7. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 026.8

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

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

#### 17.5.8. Sacubitril, valsartan - ENTRESTO (CAP) - EMEA/H/C/004062/MEA 004.8

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 004.7 [third 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]] as per the request for supplementary information (RSI) adopted in June 2020

#### [17.5.9. Sacubitril, valsartan - NEPARVIS \(CAP\) - EMEA/H/C/004343/MEA 003.5](#)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: MAH's response to MEA 003.4 [third 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]] as per the request for supplementary information (RSI) adopted in June 2020

#### [17.5.10. Simoctocog alfa - NUWIQ \(CAP\) - EMEA/H/C/002813/MEA 004.6](#)

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Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Yearly progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]

#### [17.5.11. Simoctocog alfa - VIHUMA \(CAP\) - EMEA/H/C/004459/MEA 004.5](#)

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Applicant: Octapharma AB

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Yearly progress report for study GENA-99: a prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of simoctocog alfa in patients with haemophilia A treated in routine clinical practice [final report due date expected in 2020]

#### [17.5.12. Ulipristal acetate - ESMYA \(CAP\) - EMEA/H/C/002041/MEA 018.4](#)

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Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Annika Folin

Scope: MAH's response to MEA 018.3 [fourth yearly progress report for study PGL14-001: a prospective, multinational, multicentre, non-interventional study to evaluate the long-term safety of Esmya (ulipristal acetate) in particular the endometrial safety and the current prescription and management patterns of Esmya (ulipristal acetate) in a long-term treatment setting [final clinical study report (CSR) expected in 2023]] as per the request for supplementary information (RSI) adopted in June 2020

### 17.5.13. Vedolizumab - ENTYVIO (CAP) - EMEA/H/C/002782/MEA 001.1

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Applicant: Takeda Pharma A/S

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 001 [interim analysis report for study MLN-0002-401 (listed as a category 3 study in the RMP): an international prospective, observational, cohort safety study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease [final clinical study report (CSR) expected in June 2022]] as per the request for supplementary information (RSI) adopted in July 2020

### 17.6. Others

None

### 17.7. New Scientific Advice

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

### 17.8. Ongoing Scientific Advice

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

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

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

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

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

### 18.1. Annual reassessments of the marketing authorisation

#### 18.1.1. Cerliponase alfa - BRINEURA (CAP) - EMEA/H/C/004065/S/0028 (without RMP)

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Annual reassessment of the marketing authorisation

#### 18.1.2. Galsulfase - NAGLAZYME (CAP) - EMEA/H/C/000640/S/0083 (without RMP)

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Applicant: BioMarin International Limited

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Annual reassessment of the marketing authorisation

#### 18.1.3. Nelarabine - ATRIANCE (CAP) - EMEA/H/C/000752/S/0051 (without RMP)

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Applicant: Novartis Europharm Limited

PRAC Rapporteur: Hans Christian Siersted

Scope: Annual reassessment of the marketing authorisation

#### 18.1.4. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/S/0054 (without RMP)

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Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

#### 18.1.5. Vestronidase alfa - MEPSEVII (CAP) - EMEA/H/C/004438/S/0017 (without RMP)

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Applicant: Ultragenyx Germany GmbH

PRAC Rapporteur: Eva Segovia

Scope: Annual reassessment of the marketing authorisation

### 18.2. Conditional renewals of the marketing authorisation

#### 18.2.1. Bedaquiline - SIRTURO (CAP) - EMEA/H/C/002614/R/0040 (without RMP)

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Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Conditional renewal of the marketing authorisation

#### 18.2.2. Obeticholic acid - OCALIVA (CAP) - EMEA/H/C/004093/R/0023 (without RMP)

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Applicant: Intercept Pharma International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

### 18.3. Renewals of the marketing authorisation

#### 18.3.1. Albutrepenonacog alfa - IDELVION (CAP) - EMEA/H/C/003955/R/0047 (without RMP)

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Applicant: CSL Behring GmbH



PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**18.3.2. Amlodipine, valsartan - AMLODIPINE-VALSARTAN MYLAN (CAP) - EMEA/H/C/004037/R/0008 (with RMP)**

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Applicant: Mylan S.A.S

PRAC Rapporteur: Anette Kirstine Stark

Scope: 5-year renewal of the marketing authorisation

**18.3.3. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/R/0077 (without RMP)**

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Applicant: Bristol-Myers Squibb / Pfizer EEIG

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

**18.3.4. Emtricitabine, rilpivirine, tenofovir alafenamide - ODEFSEY (CAP) - EMEA/H/C/004156/R/0049 (with RMP)**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

**18.3.5. Emtricitabine, tenofovir alafenamide - DESCOVY (CAP) - EMEA/H/C/004094/R/0051 (without RMP)**

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Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: 5-year renewal of the marketing authorisation

**18.3.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/R/0064 (without RMP)**

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Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: 5-year renewal of the marketing authorisation

**18.3.7. Migalastat - GALAFOLD (CAP) - EMEA/H/C/004059/R/0027 (with RMP)**

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Applicant: Amicus Therapeutics Europe Limited

PRAC Rapporteur: Ulla Wändel Liminga

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 26-29 October 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Sonja Hrabcik	Alternate	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Maria Popova-Kiradjieva	Member	Bulgaria	No interests declared	Full involvement
Nikica Mirošević Skvrce	Member	Croatia	No interests declared	Full involvement
Helena Panayiotopoulou	Member	Cyprus	No interests declared	Full involvement
Panagiotis Psaras	Alternate	Cyprus	No interests declared	Full involvement
Eva Jirsová	Member	Czech Republic	No interests declared	Full involvement
Jana Lukacisinova	Alternate	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Hans Christian Siersted	Alternate	Denmark	No restrictions applicable to this meeting	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Adrien Inoubli	Member	France	No interests declared	Full involvement
Tiphaine Vaillant	Alternate	France	No interests declared	Full involvement
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislawski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou	Member	Greece	No interests declared	Full involvement
Julia Pallos	Member	Hungary	No participation in final deliberations	4.1.1. Immune checkpoint inhibitors:

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			and voting on:	atezolizumab – TECENTRIQ (CAP); avelumab – BAVENCIO (CAP); cemiplimab – LIBTAYO (CAP); durvalumab – IMFINZI (CAP); ipilimumab – YERVOY (CAP); pembrolizumab – KEYTRUDA (CAP); nivolumab - OPDIVO (CAP) 4.3.2. Cefepime (NAP) 4.3.6. Immune checkpoint inhibitors: atezolizumab – TECENTRIQ (CAP); avelumab – BAVENCIO (CAP); cemiplimab – LIBTAYO (CAP); durvalumab – IMFINZI (CAP); ipilimumab – YERVOY (CAP); pembrolizumab – KEYTRUDA (CAP); nivolumab - OPDIVO (CAP) 5.3.3. Belatacept - NULOJIX (CAP) 6.1.5. Ipilimumab - YERVOY (CAP) 15.3.9. Ipilimumab - YERVOY (CAP); nivolumab - OPDIVO (CAP) 18.3.3. Apixaban - ELIQUIS (CAP)
Melinda Palfi	Alternate	Hungary	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
Guðrún Stefánsdóttir	Member	Iceland	No participation in discussion, final deliberations and voting on:	4.2.1. Cannabidiol – EPIDYOLEX (CAP); tacrolimus - ADVAGRAF (CAP), ENVARSUS (CAP), MODIGRAF (CAP), TACFORIUS (CAP); NAP 15.2.6. Tacrolimus - ADVAGRAF (CAP); MODIGRAF (CAP) 16.1.14. Gilteritinib - XOSPATA (CAP) 17.4.6. Mirabegron - BETMIGA (CAP)
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Ilaria Baldelli	Alternate	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilviniene	Member	Lithuania	No interests declared	Full involvement
Nadine Petitpain	Member	Luxembourg	No restrictions applicable to this meeting	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in final deliberations and voting on:	6.3.3 Fluconazole (NAP) 15.2.3. Iloprost - VENTAVIS (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				15.3.16. Rivaroxaban - XARELTO (CAP) 17.2.4. Interferon beta-1b - BETAFERON (CAP) 17.5.4. Damoctocog alfa pegol - JIVI (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Katarzyna Ziolkowska	Alternate	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Alexandra - Maria Spurni	Alternate	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No interests declared	Full involvement
Marek Juracka	Alternate	Slovakia	No interests declared	Full involvement
Jasmina Klopčič	Alternate	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Milou Daniel Drici	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No participation in discussion,	17.5.12. Ulipristal acetate - ESMYA (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			final deliberations and voting on:	
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Roberto Frontini	Alternate	Healthcare Professionals' Representative	No restrictions applicable to this meeting	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Ivona Bahnik Biševac	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Ivana Ljubičić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Katica Milčić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Maja Tabak Slošić	Expert - via telephone*	Croatia	No restrictions applicable to this meeting	Full involvement
Karin Erneholm	Expert - via telephone*	Denmark	No restrictions applicable to this meeting	Full involvement
Pernille Gammelgaard	Expert - via telephone*	Denmark	No interests declared	Full involvement
Marian Hjortlund Allon	Expert - via telephone*	Denmark	No interests declared	Full involvement
Moritz Sander	Expert - via telephone*	Denmark	No interests declared	Full involvement
Caroline Marie Voss	Expert - via telephone*	Denmark	No interests declared	Full involvement
Mette Juul Wikkelsø	Expert - via telephone*	Denmark	No interests declared	Full involvement
Kroot Aab	Expert - via telephone*	Estonia	No interests declared	Full involvement
Emiliano Gemma	Expert - via telephone*	France	No interests declared	Full involvement
Faustine Vidil	Expert - via telephone*	France	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
Philipp Berg	Expert - via telephone*	Germany	No interests declared	Full involvement
Dennis Lex	Expert - via telephone*	Germany	No restrictions applicable to this meeting	Full involvement
Kerstin Löschcke	Expert - via telephone*	Germany	No interests declared	Full involvement
Grainne Kirwan	Expert - via telephone*	Ireland	No interests declared	Full involvement
Sara Bangiere	Expert - via telephone*	Latvia	No restrictions applicable to this meeting	Full involvement
Gunta Pauksena	Expert - via telephone*	Latvia	No interests declared	Full involvement
Charlotte Backman	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

\* Experts were only evaluated against the agenda topics or activities they participated in

## 20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

## 21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

### **EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures**

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### **Signals assessment and prioritisation**

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources

such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

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

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

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

(Item 5 of the PRAC minutes)

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

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

(Item 6 of the PRAC minutes)

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

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

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

(Item 7 of the PRAC minutes)

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

### **Product related pharmacovigilance inspections**

(Item 9 of the PRAC minutes)

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

More detailed information on the above terms can be found on the EMA website:

<https://www.ema.europa.eu/en>