03 August 2022
EMA/591686/2022 Corr*
Human Medicines Division

List of centrally authorised products requiring a notification of a change for update of annexes

Parallel distributors are only required to inform the EMA of changes to the labelling or leaflet related to any update of the annexes of marketing authorisation once a year in their annual update application, except in cases related to safety or quality issues. The following table lists the centrally authorised products for which the EMA requires notifications of safety update before implementation.

Name	EU number	Date of communication	Rationale
Aerinaze	All presentations	15/06/2022	Update of section 4.8 of the Summary of Product Characteristics to add the adverse reaction "depressed mood" with a frequency unknown. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000963/202107), which are available on both the Commission the Agency's website**
Aerius	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website**
Azomyr	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website**
Azopt	All presentations	15/07/2022	Update of sections 4.4 and 4.8 of the SmPC to add the ADR SJS/TEN with a frequency 'not known' and a warning on SJS/TEN is considered warranted. The Package leaflet has been updated accordingly. **Parallel distributors must use the annexes dated 24/06/2022 (PSUSA/00000432/202108), which are available on both the Commission the Agency's website.**

Name	EU number	Date of communication	Rationale
Blenrep	All presentations	15/06/2022	In view of available data on pneumonitis from spontaneous reports including in one case a reasonable temporal relationship and absence of other causal explanations and in view of a non-clinical signal and plausible mechanism of action, the PRAC considers a causal relationship between belantamab mafodotin and pneumonitis is at least a reasonable possibility. Therefore, changes to the wording in section 4.4 are proposed by deleting "although a causal association has not been established" and in addition to update section 4.8 with 'pneumonitis' as an ADR. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 13/05/2022 (PSUSA/00010869/202108), which are available on the European Commission website.**

Name	EU number	Date of communication	Rationale
Bosulif	All presentations	15/05/2022	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect results from the studies B1871039 (SOB) and B1871040 (category 3); study B1871039 is A Phase 4 Safety and Efficacy Study of Bosutinib in patients with Philadelphia chromosome positive chronic myeloid leukaemia previously treated with one or more Tyrosine kinase inhibitors and study B1871040 is An open-label Bosutinib treatment extension study for subjects with chronic myeloid leukaemia (CML) who have previously participated in Bosutinib studies B1871006 or B1871008. The MAH requested deletion of the SOB from annex II of the PI and request consideration for switch of the Conditional Marketing Authorisation to a full Marketing Authorisation. The MAH is also requested the deletion of the product from the additional monitoring list. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 07/04/2022 (II/0050/G), which are available on both the Agency's and the European Commission website.**
Controloc Control	All presentations	15/06/2022	Update section 4.8 of the SmPC to update the existing term "Interstitial nephritis" to "Tubulointerstitial nephritis (TIN)" in line with the updated Company Core Data Sheet. In addition, section 4.4 of the SmPC for centralised authorised products is updated with the Excipient warning for Sodium as per EMA guideline EMA/CHMP/302620/2017/EN Rev. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 07/06/2022 (Yearly update which includes WS2154 safety scope), which are available on the European Commission website**
Copalia HCT	All presentations	15/06/2022	To update sections 4.4 and 4.8 of the SmPC in line with assessment of a PSUSA/00001662/202101 procedure on hydrochlorothiazide/spironolactone regarding

Name	EU number	Date of communication	Rationale
			the risk of acute respiratory distress syndrome (ARDS) linked to hydrochlorothiazide. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 31/03/2022 (WS2237), which are available on the Agency's website**
Cosentyx	All presentations	15/06/2022	Update of section 4.8 of the SmPC in order to add the new ADR "dyshidrotic eczema" with the frequency Uncommon based on post-marketing data. The section 4 of the package leaflet is updated accordingly **Parallel distributors must use the annexes dated 31/03/2022 (II/0084), which are available on the Agency's website**
Cresemba	All presentations	15/07/2022	Update of section 4.4 and 4.8 of the SmPC to add the adverse reaction anaphylactic reaction with a frequency not known and a warning on anaphylactic reaction. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/06/2022 (PSUSA/00010426/ 202109), which are available on the European Commission website.**
Dafiro HCT	All presentations	15/06/2022	To update sections 4.4 and 4.8 of the SmPC in line with assessment of a PSUSA/00001662/202101 procedure on hydrochlorothiazide/spironolactone regarding the risk of acute respiratory distress syndrome (ARDS) linked to hydrochlorothiazide. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 31/03/2022 (WS2237), which are available on the Agency's website**.
Dasselta	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown"

Name	EU number	Date of communication	Rationale
			Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website
Desloratadine Actavis	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on the Agency's website**
Desloratadine ratiopharm	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 09/06/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website**
Desloratadine Teva	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website**
Dexdor	All presentation	15/07/2022	Update of section 4.4 of the SmPC and PL section 2 in order to add a new warning on increased mortality in ICU patients ≤65 years old, based on results from study SPICE III (randomised controlled trial) and following the

Name	EU number	Date of communication	Rationale
			assessment of the post-authorisation measure LEG 16.4. **Parallel distributors must use the annexes dated 08/07/2022 (II/0035), which are available on both the Commission the Agency's website**
Exforge HCT	All presentations	15/06/2022	To update sections 4.4 and 4.8 of the SmPC in line with assessment of a PSUSA/00001662/202101 procedure on hydrochlorothiazide/spironolactone regarding the risk of acute respiratory distress syndrome (ARDS) linked to hydrochlorothiazide. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 31/03/2022 (WS2237), which are available on the Agency's website**.
Fycompa	All presentations	15/05/2022	Update of section 4.8 of the SmPC to add the adverse reaction hallucination with a frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 11/03/2022 (N/0062 which includes the PSUSA/9255/202007 safety scopes too), which are available on the Agency's website**
Ganfort	All presentations	15/07/2022	Update of section 4.8 of the SmPC in order to add periorbital and lid changes associated with periorbital fat atrophy and skin tightness to the list of adverse drug reactions (ADRs) with frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 31/03/2022 (T/0030 which includes the II/0038 safety scopes too), which are available on the Agency's website**.
Gardasil 9	All presentations	15/05/2022	Update of section 5.1 of the SmPC with long-term effectiveness and immunogenicity data following the final results of the Gardasil 9 long-term follow-up (LTFU) study V503-002-20

Name	EU number	Date of communication	Rationale
			listed as a category 3 study in the RMP. In addition, the applicant took the opportunity to make some minor editorial changes (spacings) and included the updated long-term follow-up data received for the qHPV vaccine following V501-167 extension study. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/03/2022 (II/0053), which are available on the Agency's website**
Glyxambi	All presentation	15/05/2022	Update section 4.8 of the SmPC and section 4 of the PL to include the side effect 'constipation' in order to align with the Jardiance PI following approval of EMEA/H/C/002677/II/0055.In addition, the following ADR have been updated in section 4.8: 'Necrotising fasciitis of the perineum (Fournier´s gangrene)' from 'not known' to 'rare'; 'Volume depletion', to add a footnote to indicate that studies with empagliflozin in patients with heart failure showed a higher frequency of volume depletion 'very common ' in patients with heart failure where half of the patients had type 2 diabetes mellitus. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 13/04/2022 (IAIN/0046 which also includes the WS2171 safety variations), which are available on the Agency's website.**
Hemlibra	All presentations	15/05/2022	Update of sections 4.4, 4.8 and 5.1 of the Product information concerning immunogenicity and loss of efficacy due to anti-emicizumab antibodies. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 10/03/2022 (II/0025), which are available on the Agency's website.**
Hexacima	All presentations	15/05/2022	Update of section 4.5 of the SmPC in order to add drug-drug interaction information regarding the co-administration of Hexyon /

Name	EU number	Date of communication	Rationale
			Hexacima with varicella vaccines based on a re-analysis of the A3L15 clinical trial varicella serological data, submitted in the initial CTD dossier. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 24/03/2022 (WS2174), which are available on the Agency's website**
Hexyon	All presentations	15/05/2022	Update of section 4.5 of the SmPC in order to add drug-drug interaction information regarding the co-administration of Hexyon / Hexacima with varicella vaccines based on a re-analysis of the A3L15 clinical trial varicella serological data, submitted in the initial CTD dossier. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 24/03/2022 (WS2174), which are available on the Agency's website**
Iclusig	All presentations	15/07/2022	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from the OPTIC study (AP24534-14-203) listed as a specific obligation in the Annex II. This is a randomised, open-label, Phase 2 trial of ponatinib in patients with chronic myeloid leukaemia to characterise the efficacy and safety of ponatibib over a range of doses; the package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/03/2022 (II/0061), which are available on the Agency's website**
Infanrix Hexa	All presentations	15/05/2022	Update of section 2 of the SmPC of Infanrix Hexa and other GSK's DTPa/dTpa combined vaccines (NAPs). In addition, the MAH took the opportunity to align the PI to the Annex to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal product for human use" (sections 2, 4.4 and 6.1 of the SmPC). The package leaflet is updated accordingly.

Name	EU number	Date of communication	Rationale
			Parallel distributors must use the annexes dated 24/03/2022 (WS2183), which are available on the Agency's website
Jevtana	All presentations	15/06/2022	Update of section 4.8 of the SmPC to add the adverse reactions nail disorder, gastrointestinal haemorrhage, ileus, gastritis, colitis, and gastrointestinal perforation, with appropriate frequencies. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000476/202106), which are available on the European Commission website.**
Keytruda	All presentations	15/07/2022	Update of section 2 of the package leaflet to add the risk of diabetic ketoacidosis, including the symptoms. **Parallel distributors must use the annexes dated 22/06/2022 (II/0111 which includes the PSUSA/00010403/202109 safety scopes) which are available on the Agency's website.**
Kisplyx	All presentations	15/07/2022	Update of section 4.8 of the SmPC of in order to add colitis to the list of ADRs with frequency uncommon, following PRAC Signal assessment of colitis with lenvatinib (EPITT no: 19691). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 07/04/2022 (WS2235), which are available on the Agency's website.**
Lemtrada	All presentations	15/07/2022	Update of section 4.4 of the SmPC to add a warning on autoimmune encephalitis and 4.8 to add the adverse reaction autoimmune encephalitis with a frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/06/2022 (PSUSA/00010055/202109), which are**

Name	EU number	Date of communication	Rationale
			available on both the European Commission website.
Mysimba	All presentations	15/07/2022	Update of section 4.4 of the SmPC to amend the existing warning on neuropsychiatric symptoms and section 4.8 SmPC to add the adverse reaction panic attack with a frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/06/2022 (PSUSA/00010366/ 202109), which are available on both the European Commission website.**
Neoclarityn	All presentations	15/06/2022	Update of section 4.8 of the SmPC and section 4 of the Package Leaflet: to add the adverse reaction "depressed mood" with a frequency unknown and to add the adverse reaction "eye dryness" with a frequency unknown" **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00000962/202107), which are available on both the Commission the Agency's website**
Nerlynx	All presentations	15/05/2022	Update of section 4.8 of the SmPC to add the adverse reaction syncope with a frequency common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 25/04/2022 (PSUSA/00010712/202107), which are available on both the European Commission and the Agency's website**
Ocaliva	All presentations	15/07/2022	Update of section 4.3 of the SmPC in order to include contraindication in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event based on the MAH's conclusion that it will not be feasible to establish the safety and efficacy of Ocaliva in these patients from either of the ongoing studies 747-302 and 747-401 listed as Specific Obligations in Annex II. Consequently,

Name	EU number	Date of communication	Rationale
			dosing instructions for patients with CP-B and CP-C cirrhosis are no longer applicable and section 4.2 has been updated accordingly. In addition, section 4.4 of the SmPC to include a new warning on monitoring and management of patients for possible progression of PBC and other hepatic adverse reactions. The MAH also took the opportunity to remove the outdated term "primary biliary cirrhosis" from section 4.1 and to make editorial changes to sections 4.8, 4.9, 5.1 and Annex IIE to improve clarity and correct typographical errors. The Package Leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/06/2022 (II/0030 which are available on both the European Commission and the Agency's website**
Oncaspar	All presentations	15/06/2022	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on the risk of osteonecrosis and to include it as an adverse drug reaction associated with pegaspargase use with an unknown frequency, following review of all available non-clinical, epidemiological and clinical data. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 02/06/2022 (IB/0047 which includes the II/0038 safety scope), which are available on the Agency's website**
Opdivo	All presentations	15/05/2022	Update of section 4.8 of the SmPC to move the PTs: "lymphopenia, leucopenia, neutropenia, thrombocytopenia and anaemia", from the SOC "Investigations" to the SOC "Blood and lymphatic system disorders", and to move the PTs: "hyperglycaemia, hypoglycaemia and weight decreased", from the SOC "Investigations" to the SOC "Metabolism and nutrition disorders". Update of section 2 of the package leaflet to add the risk of diabetic ketoacidosis, including the symptoms. **Parallel distributors must use the annexes dated 25/04/2022**

Name	EU number	Date of communication	Rationale
			(PSUSA/00010379/202107), which are available on both the European Commission and the Agency's website
Opsumit	All presentations	15/07/2022	Update of sections 4.2 and 4.4 of the SmPC to remove a sentence and a warning on the limited clinical experience in patients over the age of 75 years, following the recommendation of the EMEA/H/C/PSUSA/00010115/202010 procedure to remove 'Elderly patients' as missing information in the RMP. The Package Leaflet is being updated accordingly. In addition, the MAH took this opportunity to update the Package Leaflet to include a section on Male fertility and align it with the currently approved information in SmPC, sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety. **Parallel distributors must use the annexes dated 21/06/2022 (II/0046 which includes the II/0043 safety scopes too), which are available on the Agency's website.**
Prolia	All presentations	15/05/2022	Update of sections 4.2 and 4.4 of the SmPC to change the posology recommendation for paediatric population and add a new warning on hypercalcaemia in paediatric patients with osteogenesis imperfecta following an urgent safety measure regarding the risk of hypercalcaemia reported very commonly in ongoing clinical trials in paediatric patients with osteogenesis imperfecta (OI) treated with denosumab. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 05/05/2022 (II/0093) which are available on the European Commission website**
Revatio	All presentations	15/05/2022	Update of section 4.5 of the SmPC to add a warning about the increase in hypotension observed with concomitant use of sildenafil and

Name	EU number	Date of communication	Rationale
			Entresto (sacubitril/valsartan). The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 01/04/2022 (PSUSA/00002700/202105), which are available on both the European Commission and the Agency's website**
Rinvoq	All presentations	15/06/2022	Update of section 4.8 of the SmPC to add the adverse reaction urinary tract infection with a frequency common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00010823/202108) which are available on the Agency's website**
Samsca	All presentation	15/07/2022	Update of section 4.5 of the SmPC in order to include information on the transporter substrates P-glycoprotein, BCRP and OCT1 upon request by PRAC following the assessment of PSUSA/00002994/202105 based on final results from the drug-drug interaction studies 156-201-00233 and 156-201-00234 (to align with the Jinarc PI); the Package Leaflet is updated accordingly. **Parallel distributors must use the annexes dated 12/05/2022 (II/0046/G), which are available on the Agency's website.**
Symkevi	All presentations	15/06/2022	Update of section 4.4 of the Summary of Product Characteristics to add the warning of Elevated transaminase and hepatic injury. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 24/05/2022(PSUSA/00010730/202108), which are available on the Agency's website**
Symtuza	All presentation	15/07/2022	Update of sections 4.3 and 4.5 of the SmPC in order to update the safety information based on final results from study TMC114FD1HTX1002; this is an interventional

Name	EU number	Date of communication	Rationale
			phase 1, 2-Panel, Fixed-Sequence, Open-Label Single-Center Study to Assess the Effect of Single and Multiple Doses of Darunavir in Combination with Cobicistat or Ritonavir on the Pharmacokinetics of Single Dose Dabigatran Etexilate in Healthy Participants. The Package Leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2022 (R/0040, this includes WS2250/0043 safety scopes), which are available on both the European Commission and the Agency's website**
Tysabri	All presentation	15/06/2022	Update of section 4.6 of the SmPC to inform about the risk of anaemia in infants born to women exposed to natalizumab during pregnancy and the need to monitor the haemoglobin levels. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/05/2022 (PSUSA/00002127/202108), which are available on the Agency's website**
Vidaza	All presentations	15/07/2022	Update of section 4.2 of the SmPC in order to include a statement advising health care professionals not to interchange azacitidine formulations (injectable versus oral), and update section 4.6 of the SmPC to revise the recommended duration of contraception use for women and men. The Package Leaflet is updated accordingly." **Parallel distributors must use the annexes dated 28/04/2022 (II/0057), which are available on the Agency's website**
Vimpat	All presentations	15/07/2022	Update of section 4.6 of the SmPC to add information that lacosamide is excreted in breast milk. The Package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/07/2022 (PSUSA/00001816/202108), which are**

Name	EU number	Date of communication	Rationale
			available on the European Commission website.
Vocabria	All presentations	15/07/2022	Update of section 4.8 of the SmPC to add the adverse reactions "Type I hypersensitivity" and "urticaria, angioedema". Furthermore, as a general warning on hypersensitivity reactions in association with other integrase inhibitors is already included in section 4.4, only a small update of this section is necessary. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/06/2022 (PSUSA/00010900/202109) which are available on the Agency's website and European Commission website**
Xaluprine	All presentation	15/07/2022	Update of section 4.8 of the SmPC to add the adverse reaction erythema nodosum with a frequency Unknown. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/06/2022 (PSUSA/00001988/202109) which are available on the European Commission website**
Xeljanz	All presentations	15/06/2022	Update of section 5.3 of the SmPC to update safety information on reproductive and developmental toxicity based on final study results from an oral (Gavage) juvenile toxicity study of CP-690,550 in Sprague Dawley Rats (MEA 022) listed as a cat 3 study in the RMP. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 07/04/2022 (II/0046), which are available on the Agency's website**
Xtandi	All presentations	15/05/2022	Update of section 4.5 to add information regarding drug-drug interaction based on final results from study 9785-CL-0018 - A Phase 1 open-label study to evaluate the effect of multiple doses of enzalutamide on the pharmacokinetics of substrates of P-

Name	EU number	Date of communication	Rationale
			glycoprotein (Digoxin) and breast cancer resistant protein (Rosuvastatin) in male subjects with prostate cancer. Update of sections 4.8, 5.1 and 5.2 of the SmPC to reflect the updated safety and efficacy data from the final analysis of the 9785-CCL-0335 (ARCHES) study, a phase 3 randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of enzalutamide plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with mHSPC; In addition, the MAH took the opportunity to make minor editorial changes to section 4.8 and section 5.1 of the SmPC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 04/05/2022 (IAIN/0060, this includes both the II/0057 and II/0058 safety scopes), which are available on the Agency's website.**
Yervoy	All presentations	15/05/2022	Update of sections 4.2 and 6.6 of the SmPC to change the infusion time for ipilimumab when used as monotherapy or in combination with nivolumab in the melanoma indications. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/04/2022 (IB/0097, this includes WS2153 safety scopes), which are available on the Agency's website.**

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