15 October 2021
EMA/579235/2021
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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Name	EU number	Date of communication	Rationale
Aubagio	All presentations	15/08/2021	Update of sections 4.4 and 4.8 of the SmPC to add information on pulmonary hypertension cases and the adverse reaction pulmonary hypertension with a frequency not known. Update of section 4.8 of the SmPC to add the adverse reactions colitis with a frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/07/2021 (PSUSA/00010135/ 202009), which are available on the Agency's website.**
Blitzima	All presentations	15/10/2021	Update of section 4.5 of the SmPC to add wording on the interaction between posaconazole and all-trans retinoic acid (ATRA, or tretinoin), based on literature reports of hypercalcaemia occurring when posaconazole and ATRA were combined, highlighting the importance of monitoring ATRA's side effects when used in combination with drugs inhibiting the cytochrome P450 enzymes. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/08/2021 (PSUSA/00002652/202011), which are available on the Agency's website.**
Bosulif	All presentations	15/10/2021	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update safety and efficacy information based on final results from study B18711053. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/07/2021 (II/0048), which are available on the Agency's website**
Brilique	All presentations	15/10/2021	Update of the SmPC in order to add central sleep apnoea including Cheyne-Stokes respiration as a new warning in section 4.4. and in the list of adverse drug reactions (ADRs) section 4.8 with frequency not known, following collection of post-marketing data. The package leaflet is updated accordingly.

Name	EU number	Date of communication	Rationale
			Parallel distributors must use the annexes dated 29/09/2021 (IB/0053 which includes the II/0050 safety variations), which are available on the European Commission website.
Brintellix	All presentations	15/10/2021	Update of section 4.8 of the SmPC to add the adverse reactions headache and hyperprolactinaemia with a frequency not known, and hyperhidrosis with a frequency common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/09/2021 (IB/0031 which includes the PSUSA/10052/202009 safety variations), which are available on the Agency's website**
Emgality	All presentations	15/08/2021	Update of section 4.4 of the SmPC to add information that serious hypersensitivity reactions occur mainly within 1 day after galcanezumab administration, however, several cases have occurred also within days or within several weeks. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/07/2021 (PSUSA/00010733/ 202009), which are available on both the European Commission and the Agency's website.**
Epidyolex	All presentations	15/08/2021	Update of sections 4.2 and 6.6 of the SmPC in order to add information regarding enteral administration using nasogastric and gastrostomy tubes. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/06/2021 (II/0007), which are available on the Agency's website.**
Esbriet	All presentations	15/08/2021	Update of section 4.8 of the SmPC to revise the MeDRA frequency categories for some adverse drug reactions (ADR) and to combine the ADR 'anorexia' with the preferred term 'decreased appetite' based on a safety update report previously submitted in variation

Name	EU number	Date of communication	Rationale
			EMEA/H/C/2154/II/0021. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 10/06/2021 (II/0070), which are available on the Agency's website.**
Exjade	All presentations	15/10/2021	The product information has been updated to remove discrepancies between SmPC and PL in sections `Pregnancy and breast-feeding' and section `Other medicines and EXJADE'. Removal of the important identified risk, Severe cutaneous adverse reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms) Removal of the expedited reporting requirement for the serious adverse drug reactions (ADRs), increase in hepatic enzymes >10 x upper limit of normal (ULN), serious rise in creatinine, results of renal biopsies, cataracts, hearing loss, gallstones as agreed during PRAC PSUR. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 15/09/2021 (YU which includes the II/0075 safety variations) which are available on the European Commission website.**
Herceptin	All presentations	15/10/2021	Update of sections 4.2 and 4.4 of the SmPC (SC formulation) in order to modify the administration instructions by shortening observation time and including mild injection-related symptoms management based on final results from study SafeHER (MO28048) listed as a category 3 study in the RMP; this is a Phase III prospective, two Cohort nonrandomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Herceptin as adjuvant therapy in patients with operable HER2- positive early breast cancer. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/08/2021 (IB/0175/G which includes the II/0168 safety variations),**

Name	EU number	Date of communication	Rationale
			which are available on the Agency's website.
Imbruvica	All presentations	15/10/2021	Update of section 4.4 of the SmPC to add a warning on the assessment prior to treatment and monitoring of the liver function and viral hepatitis status. Update of section 4.8 of the SmPC to add the adverse reaction Eye haemorrhage with a frequency uncommon and addition of the information that in some cases loss of vision occurred. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/08/2021 (PSUSA/00010301/202011), which are available on the both the European Commission and the Agency's website.**
Jakavi	All presentation	15/08/2021	Update of sections 4.2 and 5.1 of the SmPC in order to update the posology and the method of administration as well as to include information on the A2201/EXPAND study CINC424A2201. The changes are based on final results of a Category 3 clinical study, phase Ib to fulfil an RMP post-approval commitment. This is a dose-finding study intended to establish the maximum safe starting dose (MSSD) of ruxolitinib tablets administered orally to patients with myelofibrosis (MF) in the previous unstudied population of patients who had baseline platelet counts between ≥50×109/L and <100×109/L. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/06/2021 (II/0050), which are available on both the European Commission and the Agency's website.**
Lorviqua	All presentations	15/08/2021	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to include hypertension and hyperglycaemia as new adverse drug reactions (ADRs) with frequency common and very common respectively together with recommended dose modifications and warnings, based on data from Phase 3 study B7461006, comparing lorlatinib versus

Name	EU number	Date of communication	Rationale
			crizotinib for the first-line treatment of advanced ALK-positive NSCLC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/07/2021 (II/0013), which are available on both the European Commission and the Agency's website.**
Mabthera	All presentations	15/10/2021	Update of section 4.5 of the SmPC to add wording on the interaction between posaconazole and all-trans retinoic acid (ATRA, or tretinoin), based on literature reports of hypercalcaemia occurring when posaconazole and ATRA were combined, highlighting the importance of monitoring ATRA's side effects when used in combination with drugs inhibiting the cytochrome P450 enzymes. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/08/2021 (PSUSA/00002652/202011), which are available on both the European Commission and the Agency's website.**
Mekinist	All presentations	15/10/2021	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to modify administration instructions (pyrexia dose modification guidance in the Tafinlar and Mekinist SmPC). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/08/2021 (WS/2070), which are available on both the European Commission and Agency's website.**
Noxafil	All presentations	15/10/2021	Update of section 4.5 of the SmPC to add wording on the interaction between posaconazole and all-trans retinoic acid (ATRA, or tretinoin), based on literature reports of hypercalcaemia occurring when posaconazole and ATRA were combined, highlighting the importance of monitoring ATRA's side effects when used in combination with drugs inhibiting the cytochrome P450 enzymes. The package leaflet is updated accordingly.

Name	EU number	Date of communication	Rationale
			Parallel distributors must use the annexes dated 18/08/2021 (PSUSA/00002480/202010), which are available on both the European Commission and the Agency's website
Ofev	All presentations	15/10/2021	Update of section 4.4 of the SmPC to add a warning on thrombotic microangiopathy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/08/2021 (PSUSA/00010319/202010), which are available on both the European Commission and the Agency's website**
Rapamune	All presentations	15/08/2021	Update of 'Other possible interactions' of section 4.5 of the SmPC to add the interaction between sirolimus and letermovir. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/07/2021 (PSUSA/00002710/ 202009), which are available on both the European Commission and Agency's website.**
Revlimid	All presentations	15/10/2021	Update of section 4.4 of the SmPC to update a warning on tumour lysis syndrome in view of available data from spontaneous reports in myelodysplastic syndrome indication. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 16/09/2021 (PSUSA/00001838/202012), which are available on the European Commission website.**
Rydapt	All presentations	15/10/2021	Update of section 4.4 of the SmPC to clarify the non-infectious aetiology of pneumonitis and of section 4.8 of the SmPC to add the adverse reactions pneumonitis, interstitial lung disease and electrocardiogram QT prolonged. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/08/2021 (PSUSA/00010638/202010), which are**

Name	EU number	Date of communication	Rationale
			available on both the European Commission and Agency's website.
SonoVue	All presentations	15/10/2021	Update of section 4.4 of the SmPC to amend the current warning regarding hypersensitivity reactions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/08/2021 (PSUSA/00002822/202009), which are available on both the European Commission and Agency's website.**
Stivarga	All presentations	15/10/2021	Update of section 4.8 of the Summary of Product Characteristics (SmPC) to include severe liver injury (including hepatic failure) under system organ class (SOC) hepatobiliary disorders to the list of adverse drug reactions (ADRs). Section 4.4 of the SmPC is also updated to add hepatic failure to the exiting hepatic effects. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/08/2021 (PSUSA/00010133/202009), which are available on both the European Commission and Agency's website.**
Sunosi	All presentations	15/10/2021	Update of section 4.8 of the SmPC in order to add hypersensitivity reactions to the list of adverse drug reactions (ADRs) following confirmation of a post-marketing safety signal for hypersensitivity. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 01/07/2021 (II/0009), which are available on the Agency's website**
Tafinlar	All presentations	15/10/2021	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to modify administration instructions (pyrexia dose modification guidance in the Tafinlar and Mekinist SmPC). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/08/2021 (WS/2070), which are available on both the European Commission and Agency's website**

Name	EU number	Date of communication	Rationale
Tecentriq	All presentations	15/10/2021	Update of section 4.2 of the SmPC in order to harmonise the atezolizumab posology regimen of 840 mg every 2 weeks, 1200 mg every 3 weeks and 1680 mg every 4 weeks administered as an IV infusion across the currently authorised indications of NSCLC, ES-SCLC, TNBC and HCC, based on PK modelling and simulation data. As a consequence of the harmonised dose schedules, the MAH is applying for a combined SmPC and PL. **Parallel distributors must use the annexes dated 20/08/2021 (II/0060), which are available on the Agency's website**
Thalidomide Celgene	All presentations	15/08/2021	Update of section 4.4 of the SmPC to add a warning on thyroid disorders. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/07/2021 (PSUSA/00002919/ 202010), which are available on both the European Commission and Agency's website.**
Truxima	All presentations	15/10/2021	Update of section 4.5 of the SmPC to add wording on the interaction between posaconazole and all-trans retinoic acid (ATRA, or tretinoin), based on literature reports of hypercalcaemia occurring when posaconazole and ATRA were combined, highlighting the importance of monitoring ATRA's side effects when used in combination with drugs inhibiting the cytochrome P450 enzymes. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 02/09/2021 (WS/2123 which includes the PSUSA/00002652/202011 safety update scope), which are available on the Agency's website.**
Tysabri	All presentations	15/10/2021	Update of section 4.2 of the SmPC of Tysabri 300 mg IV in order to modify administration instructions based on a review of clinical study database and global safety database reports. The package leaflet (section 2) is updated accordingly Update of section 4.6 of the SmPC

Name	EU number	Date of communication	Rationale
			in order to update information on pregnancy following a safety signal assessment of cases of neonatal thrombocytopenia that may be associated with natalizumab treatment. To update existing data in SmPC Section 4.4, 4.8 of Tysabri 150 mg solution for injection in pre-filled syringe following the same update for the 300 mg concentrate for solution for infusion, the PL was updated accordingly. In addition to the changes approved during the PSUR this application proposes the addition of `thrombocytopenia and immune thrombocytopenic purpura (ITP)' to the ADR tables for both Tysabri IV and SC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/08/2021 (IB/0128 which also includes the scopes II/0123 and 27), which are available on the Agency's website.**
Vimpat	All presentations	15/08/2021	Update of section 4.8 of the SmPC in order to add dyskinesia to the list of adverse drug reactions (ADRs) with frequency uncommon following the outcome of continuous safety signal assessments of the relevant reported clinical and post-marketing cases. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 10/06/2021 (WS/2066), which are available on the Agency's website.**
Viramune	All presentations	15/10/2021	Update of sections 4.4 and 5.2 of the SmPC in order to remove wording on precautionary measures related to reassuring that tablet remnants in faeces have no impact on the therapeutic response of Viramune, based on additional clinical and pharmacovigilance data that have become available; the package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/07/2021 (II/0147), which are available on the Agency's website**

Name	EU number	Date of communication	Rationale
Votrient	All presentations	15/10/2021	Update of section 4.8 of the SmPC in order to add hepatic failure to the list of adverse reactions reported in patients with soft tissue sarcoma (STS) with the frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/09/2021 (IAIN/0070 which includes the II/0067/G safety scope too), which are available on the Agency's website.**
Xarelto	All presentations	15/10/2021	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following the final results from the VOYAGER PAD study, a multicentre, randomised, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularisation procedures. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/08/2021 (II/0081) which are available on the European Commission website.**
Yondelis	All presentations	15/10/2021	Update of section 4.8 of the SmPC in order to revise the frequency of ADRs based on a pooled safety analysis. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/07/2021 (II/0063), which are available on the Agency's website.**
Zejula	All presentations	15/08/2021	Update of section 4.8 of the SmPC to add the adverse reaction cognitive impairment (e.g., memory impairment, concentration impairment) with a frequency of common. Since loss of concentration influences the ability to drive, section 4.7 is updated accordingly. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/07/2021 (PSUSA/00010655/**

Name	EU number	Date of communication	Rationale
			202009), which are available on both the European Commission and Agency's website.

Index: