15 September 2017
EMA/608855/2017
Committees and Inspections

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 a notification of change before implementation.

Name	EU number	Date of communication	Rationale
Aerius	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add the adverse reaction abnormal behaviour and aggression with a frequency unknown; and to add the adverse reaction QT prolongation with a frequency unknown. Update of section 4.4 of the SmPC to add a warning regarding convulsions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2017 (PSUSA/962/201607), which are available on the Agency's website**.
Aranesp	All presentations	15/09/2017	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on severe cutaneous conditions including Erythema multiform and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (II/141), which are available on the European Commission website**.

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Aubagio	All presentations	15/07/2017	Update of section 4.8 of the SmPC to include the adverse drug reactions interstitial lung disease (ILD), acute hepatitis, and asthenia and nails disorders with a frequency not known. Furthermore, alanine aminotransferase (ALT) increase, gamma-glutamyl transferase (GGT) increase and aspartate aminotransferase increase are moved from the SOC Investigations to the newly introduced SOC hepatobiliary disorders with the same frequencies as before. Finally, the existing warning on respiratory reactions in section 4.4 of the SmPC has been updated in relation to ILD. The package leaflet is updated accordingly. In addition, certain side-effects in the package leaflet have also been moved under serious side-effects. **Parallel distributors must use the annexes dated 15/06/2017 (PSUSA/10135/201609), which are available on the Agency's website**.
Azomyr	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add the adverse reaction abnormal behaviour and aggression with a frequency unknown; and to add the adverse reaction QT prolongation with a frequency unknown. Update of section 4.4 of the SmPC to add a warning regarding convulsions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2017 (PSUSA/962/201607), which are available on the Agency's website**.
CoAprovel	All presentations	15/09/2017	Update of section 4.8 of the SmPC to include thrombocytopenia in the list on adverse reactions reported with the use of irbesartan alone under the System Organs Class (SOC) of blood and lymphatic system disorders with frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/08/2017 (PSUSA/1653/201609), which are available on the European Commission website**.

Dasselta	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add the adverse reaction abnormal behaviour and aggression with a frequency unknown; and to add the adverse reaction QT prolongation with a frequency unknown. Update of section 4.4 of the SmPC to add a warning regarding convulsions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/05/2017 (PSUSA/962/201607), which are available on the Agency's website**.
Evra	All presentations	15/07/2017	Update of sections 4.3, 4.4, and 4.5 of the SmPC in line with class labelling agreed by the CMDh, in order to add a contraindication against concomitant use of EVRA with direct-acting antiviral (DAA) agents that contain paritaprevir/ritonavir, ombitasvir, and/or dasabuvir, a warning and drug-drug interaction information, respectively. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/06/2017 (II/0041), which are available on the European Commission website**.
Exjade	All presentations	15/09/2017	Update of section 4.4 of the SmPC to amend the current warning on skin disorders to include severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and update of section 4.8 of the SmPC to add the new adverse drug reaction 'DRESS' with a 'rare' frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/08/2017 (PSUSA/939/201610), which are available on the European Commission website**
Ferriprox	All presentations	15/07/2017	Update of section 4.4 and 4.8 of the SmPC to add a statement on the risk of neurological disorders which can occur in children. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2017 (PSUSA/0940/201608), which are available on the European Commission website**.

Forxiga	All presentations	15/07/2017	Update of section 4.8 of the SmPC in order to add rash as new skin and subcutaneous tissue adverse reactions occurring with the frequency of common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/04/2017 (WS/1055), which are available on the Agency's website**.
Imbruvica	All presentations	15/09/2017	Update of section 4.4 and 4.8 of the SmPC to add 'hepatitis B reactivation'. Update section 4.4 of the SmPC to add cardiac arrhythmia to the existing Atrial fibrillation/flutter The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (PSUSA/10301/201611), which are available on the European Commission website**
Incruse	All presentations	15/08/2017	Update of section 4.8 of the SmPC and relevant section of the PL to add hypersensitivity reactions including rash, urticaria, pruritus as uncommon and anaphylaxis and angioedema as rare adverse reactions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 13/07/2017 (PSUSA/10263/201610), which are available on the Agency's website**.
Intelence	All presentations	15/09/2017	Update of sections 4.3, 4.4 and 4.5 of the SmPC to include additions to the drug-drug interaction (DDI) information of etravirine with hepatitis C virus (HCV) direct-acting antivirals (DAAs) elbasvir/grazoprevir, daclastavir and simeprevir and human immunodeficiency virus (HIV) protease inhibitors (PIs) atazanavir/cobicistat and darunavir/cobicistat, following the same changes in medicinal products containing these active substances. Section 4.9 of the SmPC is also updated with regard to treatment of etravirine overdose. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 13/07/2017 (II/0050), which are available on the Agency's website**.

IntronA	All presentations	15/09/2017	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on HCV/HBV co-infection and to add hepatitis B reactivation in HCV/HBV co-infected patients as an ADR, respectively, based on post marketing adverse experience. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/06/2017 (WS/1105), which are available on the Agency's website**.
Jardiance	All presentations	15/08/2017	Update of section 4.8 of the SmPC to add the adverse drug reactions angioedema with a frequency category not known, rash with a common frequency and urticaria with an uncommon frequency. Section 4.4 is also updated to reflect the occurrence of fatal cases of diabetic ketoacidosis. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/07/2017 (PSUSA/10388/201610), which are available on the European Commission website**.
Kadcyla	All presentations	15/07/2017	To update the SmPC sections 4.4 and 4.8 to introduce a new warning and a detailed description regarding haemorrhage (not necessarily associated with thrombocytopenia). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 11/05/2017 (II/0031), which are available on the Agency's website**.
Kaletra	All presentations	15/09/2017	Update of sections 4.3 and 4.5 of the SmPC in order to add new contraindications and interaction information of lopinavir/ritonavir with venetoclax, with elbasvir/grazoprevir and with ombitasvir/paritaprevir/ritonavir with or without dasabuvir based on the company's core data sheet. The package Leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (WS/1178), which are available on the European Commission website**

Karvezide	All presentations	15/09/2017	Update of section 4.8 of the SmPC to include thrombocytopenia in the list on adverse reactions reported with the use of irbesartan alone under the System Organs Class (SOC) of blood and lymphatic system disorders with frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (PSUSA/1653/201609), which are available on the European Commission website**.
Keytruda	All presentations	15/09/2017	Update of section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions. Update sections 4.4 and 4.8 of the SmPC to include the risk of myocarditis that has been reported in patients treated with nembrolizumab The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (II/23/G), which are available on the European Commission website**.
Lumigan	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add the adverse reactions eye discharge, lacrimation increased, eye oedema and foreign body sensation in eyes. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/05/2017 (II/0052), which are available on the Agency's website**.
Mekinist	All presentations	15/09/2017	Update of section 4.8 of the SmPC to add the adverse reaction 'photosensitivity reaction' with a frequency 'common' for the trametinib/dabrafenib combination therapy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/08/2017 (PSUSA/10262/201611), which are available on the European Commission website**.
Norvir	All presentations	15/09/2017	Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication regarding the interaction between ritonavir and venetoclax based on the company's core data sheet. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/08/2017 (II/147), which are available on the European Commission website**.

Noxafil	All presentations	15/07/2017	Update of sections 4.4 and 4.5 of the SmPC in order to strengthen the current warning on interaction of posaconazole with vincristine. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/04/2017 (II/0048), which are available on the Agency's website**.
Ofev	All presentations	15/08/2017	Update of section 4.4 of the SmPC to amend the current warning on diarrhoea to add that it can lead to dehydration and electrolyte disturbances and update of section 4.8 of the SmPC to add 'dehydration' as a new ADR with an 'uncommon' frequency. Update of section 4.4 of the SmPC to amend the current warning on haemorrhage and update of section 4.8 to include a cross reference to section 4.4 of the SmPC for the ADR 'bleeding'. Update of section 4.4 of the SmPC to amend the current warning on gastrointestinal perforations. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/07/2017 (PSUSA/00010319/201610), which are available on the European Commission website**.
PegIntron	All presentations	15/09/2017	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on HCV/HBV co-infection and to add hepatitis B reactivation in HCV/HBV co-infected patients as an ADR, respectively, based on post marketing adverse experience. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/06/2017 (WS/1105), which are available on the Agency's website**.
Prolia	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to include osteonecrosis of external auditory canal as an adverse drug reaction and to introduce a relevant wording. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/06/2017 (PSUSA/954/201609), which are available on the European Commission website**.

Relvar Ellipta	All presentations	15/09/2018	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and include data from the HZC113782 (SUMMIT) study (designed to investigate whether FF/VI- Furoate/Vilanterol could improve survival in patients with moderate chronic obstructive pulmonary disease (COPD) who had, or were at increased risk for cardiovascular disease (CV)). Update of section 4.8 of the SmPC in order to add "paradoxical bronchospasm" to the list of adverse reactions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/05/2017 (WS/1157), which are available on the Agency's website**
Revinty Ellipta	All presentations	15/08/2017	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and include data from the HZC113782 (SUMMIT) study (designed to investigate whether FF/VI- Furoate/Vilanterol could improve survival in patients with moderate chronic obstructive pulmonary disease (COPD) who had, or were at increased risk for cardiovascular disease (CV)). Update of section 4.8 of the SmPC in order to add "paradoxical bronchospasm" to the list of adverse reactions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/04/2017 (WS/1101), which are available on the Agency's website**
Sebivo	All presentations	15/07/2017	Update of section 4.4 of the SmPC to reinforce the current warning on lactic acidosis and update of section 4.8 of the SmPC to delete from the adverse drug reaction lactic acidosis the reference to a secondary event often associated with serious conditions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/06/2017 (PSUSA/2880/201608), which are available on the Agency's website**.
Stivarga	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add dehydration with the frequency common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 12/06/2017 (PSUSA/10133/201609), which are available on the Agency's website**.

Synjardy	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add the adverse drug reactions angioedema with a frequency category not known, rash with a common frequency and urticaria with an uncommon frequency. Section 4.4 is also updated to reflect the occurrence of fatal cases of diabetic ketoacidosis. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/07/2017 (PSUSA/10388/201610), which are available on the European Commission website**
Tecfidera	All presentations	15/07/2017	To update section 4.8 of the SmPC to include liver function abnormalities as an adverse event, observed in the post-marketing setting, and to clarify events not observed in placebo-controlled studies. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/05/2017 (II/0035), which are available on the Agency's website**.
Trulicity	All presentations	15/07/2017	Update of section 4.8 of the SmPC to add hypersensitivity as adverse reaction with a frequency uncommon. Anaphylactic reaction and angioedema are also being added, with a frequency rare. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/06/2017 (PSUSA/10311/201609), which are available on the Agency's website**.

Tyverb	All presentations	15/09/2017	Update of sections 4.4, 4.8, and 5.1 of the SmPC in order to add a warning on concentration-dependent increase of the QTc interval, concomitant use of CYP3A4 inhibitors, a strengthened recommendation of ECG monitoring (section 4.4), to add to the tabulated list of adverse reactions 'Ventricular arrhythmias/Torsades de Pointes, electrocardiogram QT prolonged' (frequency not known)(section 4.8) and to update safety information (section 5.1) following the submission of study report EGF114271 (a phase IV placebo controlled single sequence crossover study to evaluate the effect of repeat oral doses of lapatinib on cardiac repolarization in patients with advanced cancer. Update of section 4.8 of the SmPC reflecting, in the tabulated list of adverse reactions, amongst serious cutaneous reactions, Stevens - Johnson syndrome and toxic epidermal necrolysis has been observed (frequency not known). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/07/2017 (II/0048/G), which are available on the Agency's website**
Vargatef	All presentations	15/09/2017	Update of section 4.4 of the SmPC to amend the current warning on diarrhoea to add that it can lead to dehydration and electrolyte disturbances. Update of section 4.4 of the SmPC to amend the current warning on haemorrhage and update of section 4.8 to include a cross reference to section 4.4 of the SmPC for the ADR 'bleeding' and to update the description of the selected adverse event 'bleeding'. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/08/2017 (PSUSA/00010318/201611), which are available on the European Commission website**.
ViraferonPeg	All presentations	15/09/2017	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on HCV/HBV co-infection and to add hepatitis B reactivation in HCV/HBV co-infected patients as an ADR, respectively, based on post marketing adverse experience. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/06/2017 (WS/1105), which are available on the Agency's website**.

Xagrid	All presentations	15/07/2017	Update of section 4.4 of the SmPC to add a warning on pulmonary hypertension and section 4.8 to change the frequency of pulmonary hypertension to uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/06/2017 (PSUSA/208/201609), which are available on the European Commission website**.
Xarelto	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to add information regarding Stevens-Johnson syndrome/toxic epidermal necrolysis. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/06/2017 (PSUSA/2653/201609), which are available on the Agency's website**.
Xgeva	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to include osteonecrosis of external auditory canal as an adverse drug reaction and to introduce a relevant wording. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/06/2017 (PSUSA/9119/201609), which are available on the European Commission website**.
Xigduo	All presentations	15/07/2017	Update of section 4.8 of the SmPC in order to add rash as new skin and subcutaneous tissue adverse reactions occurring with the frequency of common. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/04/2017 (WS/1055), which are available on the Agency's website**.
Yondelis	All presentations	15/07/2017	To update section 4.4 and 4.8 of the SmPC to introduce a warning on capillary leak syndrome (CLS) with frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/06/2017 (PSUSA/3001/201609), which are available on the Agency's website**.

Zoledronic acid Hospira	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to add a warning on osteonecrosis of other anatomical sites and add this adverse reaction with a frequency very rare. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/06/2017 (PSUSA/3149/201608), which are available on the Agency's website**.
Zoledronic acid medac	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to add a warning on osteonecrosis of other anatomical sites and add this adverse reaction with a frequency very rare. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/06/2017 (PSUSA/3149/201608), which are available on the Agency's website**.
Zometa	All presentations	15/07/2017	Update of sections 4.4 and 4.8 of the SmPC to add a warning on osteonecrosis of other anatomical sites and add this adverse reaction with a frequency very rare. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 15/06/2017 (PSUSA/3149/201608), which are available on the Agency's website**.

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