15 June 2017
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Compliance and Inspection

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
Aclasta	All presentations	15/05/2017	Update of section 4.8 of the summary of product characteristics (SmPC) in order to add the adverse reaction hypophosphataemia with a frequency rare based on post-marketing spontaneous reports and internal databases. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (II/0068), which are available on the Agency's website**.

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Aerinaze	All presentations	15/06/2017	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 in the table other adverse reactions reported for desloratadine during the post-marketing period 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 22/05/2017 (PSUSA-963-201607), which are available on the Agency's website**.
Briviact	All presentations	15/05/2017	Update of section 4.8 of the SmPC to add safety information regarding the risks of Type I hypersensitivity and an update of section 4 of the package leaflet accordingly. **Parallel distributors must use the annexes dated 20/04/2017 (PSUSA/10447/201607), which are available on the Agency's website**.
Controloc Control	All presentations	15/05/2017	Update of sections 4.3, 4.4, 4.5, 4.6 and 4.8 of the SmPC to reflect that co-administration with HIV protease inhibitors is contraindicated (not only atazanavir), to include a warning about the reduction of the absorption of vitamin B12, and a warning about the increased risk of bone fractures and hypomagnesemia, to include drug interactions with HIV protease inhibitors in section 4.5 of the SmPC, to include that animal studies have shown excretion of pantoprazole in breast milk, and to include fracture of wrist, hip and spine as undesirable effects with unknown frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/04/2017 (WS/1041), which are available on the European Commission website**.
Cosentyx	All presentations	15/04/2017	Update of section 4.8 of the SmPC to add mucosal and cutaneous candidiasis (including oesophageal candidiasis) with unknown frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/03/2017 (PSUSA/10341/201606), which are available on the Agency's website**.

Cotellic	All presentations	15/06/2017	Update of section 4.2, 4.4 and 4.8 of the SmPC to add the risks of haemorrhage and rhabdomyolysis / CPK elevations, warnings and dose recommendations. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2017 (PSUSA/10450/201608), which are available on the European Commission website**.
Desloratadine Actavis	All presentations	15/06/2017	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**.
Desloratadine ratiopharm	All presentations	15/06/2017	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**.
Desloratadine Teva	All presentations	15/06/2017	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 European Commission website**.

Dynastat	All presentations	15/05/2017	Update of section 4.4 of the SmPC in order to update the safety information related to alcohol use and gastrointestinal (GI) risk. Update of section 4.6 of the SmPC in order to update the safety information related to oligohydramnios if the product is used during second or third trimester of pregnancy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/02/2017 (II/0068/G), which are available on the Agency's website**.
Effentora	All presentations	15/06/2017	Update of sections 4.4 and 4.5 of the SmPC in order to add a warning on increased risk of increased depressant effects with the concomitant use of alcohol and possibility of a fatal outcome with concomitant use of other CNS depressants following a cumulative review on spontaneous reporting and literature review of these risks. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 09/03/2017 (II/0045), which are available on the Agency's website**.
Enbrel	All presentations	15/06/2017	Update of section 4.8 of the SmPC in order to change the frequency category of the adverse drug reaction elevated liver enzymes from rare to uncommon and to add some further details on the frequency of elevated liver enzymes reported adverse drug reactions with etanercept in double-blind controlled trials with or without concomitant methotrexate use, following the assessment of Enbrel (etanercept) PSUSA/1295/ 201602. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (II/0204), which are available on the Agency's website**.
Evotaz	All presentations	15/06/2017	Update of section 4.6 of the SmPC to add information that atazanavir is detected in human milk. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/04/2017 (PSUSA/10404/201607), which are available on the Agency's website**.

Exviera	All presentations	15/05/2017	Update of sections 4.4 and 4.5 of the SmPC to include a warning on the concomitant use of sirolimus and everolimus with dasabuvir and ombitasvir/paritaprevir/ritonavir and to update the information on the drug-drug interaction with sirolimus and everolimus. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1079), which are available on the Agency's website**.
Giotrif	All presentations	15/05/2017	Update of section 5.1 of the SmPC in order to update the information about the major mechanism of acquired resistance to afatinib. In addition, the marketing authorisation holder (MAH) took the opportunity to add the side effects itching and dry skin with frequency very common to the package leaflet to bring it in line with the SmPC. The package leaflet is updated. **Parallel distributors must use the annexes dated 23/02/2017 (II/0022), which are available on the Agency's website**.
Gonal-f	All presentations	15/06/2017	Update of the SmPC section 4.8 to indicate that thromboembolism can occur both in association with and separate from ovarian hyperstimulation syndrome (OHSS). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 30/03/2017 (II/0136), which are available on the Agency's website**.
HyQvia	All presentations	15/05/2017	Update of section 4.2 and 4.8 of the SmPC in order to add information on infusion site leakage. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (II/0032), which are available on the Agency's website**.
Invokana	All presentations	15/05/2017	Update of section 4.4 of the SmPC in order to update the safety information: the term 'and fatal' is added when describing diabetic ketoacidosis cases that have been reported. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/04/2017 (II/0026), which are available on the European Commission website**.

Jentadueto	All presentations	15/05/2017	Update of section 4.4 of the SmPC to add the adverse drug reaction bullous pemphigoid. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1140), which are available on the Agency's website**.
Jevtana	All presentations	15/04/2017	Update of section 4.8 of the SmPC to add the adverse drug reaction cystitis due to radiation recall phenomenon with an uncommon frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 03/04/2017 (II/34), which are available on the European Commission website**.
Keytruda	All presentations	15/05/2017	Update of section 4.4 of the SmPC to amend existing warnings on immune-related adverse reactions. In addition, the MAH took the opportunity to revise the instructions for handling and storage after reconstitution in SmPC sections 6.3 and 6.6 for increased clarity. The package leaflet has been updated accordingly. **Parallel distributors must use the annexes dated 02/02/2017 (II/0013), which are available on the Agency's website**.
Kisplyx	All presentations	15/05/2017	Update of section 4.8 of the SmPC to add the adverse events cholecystitis with frequency common, and the adverse events pancreatitis, amylase increased and lipase increased with frequencies uncommon, common and common, respectively. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1123), which are available on the Agency's website**.
Lenvima	All presentations	15/05/2017	Update of section 4.8 of the SmPC to add the adverse events cholecystitis with frequency common, and the adverse events pancreatitis, amylase increased and lipase increased with frequencies uncommon, common and common, respectively. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1123), which are available on the Agency's website**.

Neoclarityn	All presentations	15/06/2017	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 European Commission website**.
Nulojix	All presentations	15/04/2017	Update of section 4.2, 4.4 and 4.8 of the SmPC to reflect that a case of anaphylaxis during belatacept infusion has now been reported. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/03/2017 (PSUSA/311/201606), which are available on the European Commission website**.
Pantoloc Control	All presentations	15/05/2017	Update of sections 4.3, 4.4, 4.5, 4.6 and 4.8 of the SmPC to reflect that co-administration with HIV protease inhibitors is contraindicated (not only atazanavir), to include a warning about the reduction of the absorption of vitamin B12, and a warning about the increased risk of bone fractures and hypomagnesemia, to include drug interactions with HIV protease inhibitors in section 4.5 of the SmPC, to include that animal studies have shown excretion of pantoprazole in breast milk, and to include fracture of wrist, hip and spine as undesirable effects with unknown frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/04/2017 (WS/1041), which are available on the European Commission website**.
Picato	All presentations	15/05/2017	Update of sections 4.4 of the SmPC to add a warning on keratoacanthoma and of section 5.1 of the SmPC to include information on the high incidence of keratoacanthoma observed in study LP0105-1020 (large treatment area study). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/04/2017 (PSUSA/10035/201607), which are available on the European Commission website**.

Prezista	All presentations	15/05/2017	Update of sections 4.3 and 4.5 of the SmPC with contra-indication and information of drug-drug interactions of boosted darunavir with elbasvir/grazoprevir (Zepatier) and with lurasidone (Latuda). The package leaflet was updated accordingly. **Parallel distributors must use the annexes dated 23/02/2017 (WS/1107/G), which are available on the Agency's website**.
Rapamune	All presentations	15/05/2017	Update of section 4.4 of the SmPC to update the current warning on angioedema to include a possible dose-dependent effect between sirolimus and angioedema based on post-marketing data. Update of section 4.8 of the SmPC to include neuroendocrine carcinoma of the skin as new adverse drug reaction (ADR) with a frequency not known and to replace the ADR skin cancer by non-melanoma skin cancer and malignant melanoma with a common and uncommon frequency respectively, based on post-marketing data. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/02/2017 (II/0163/G), which are available on the Agency's website.**
Revestive	All presentations	15/06/2017	Update of sections 4.3, 4.4, and 4.8 of the SmPC in order to update the safety information in line with updated CCDS following review of the MAH's safety database. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (II/0032), which are available on the Agency's website.**
Rezolsta	All presentations	15/05/2017	Update of sections 4.3 and 4.5 of the SmPC with contra-indication and information of drug-drug interactions of boosted darunavir with elbasvir/grazoprevir (Zepatier) and with lurasidone (Latuda). The package leaflet was updated accordingly. **Parallel distributors must use the annexes dated 23/02/2017 (WS/1107/G), which are available on the Agency's website**.

Rotarix	All presentations	15/05/2017	Update of section 4.8 of the SmPC to modify the description of the risk of intussusception. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/04/2017 (PSUSA/2665/201607), which are available on the European Commission website**.
Simponi	All presentations	15/05/2017	Update of section 4.4 of the SmPC in order to include reports of Merkel cell carcinoma in patients treated with TNF blocking agents including Simponi. In addition the frequency of this ADR has been reclassified from not known to rare in section 4.8 of the SmPC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 02/02/2017 (II/0072), which are available on the Agency's website**.
Soliris	All presentations	15/05/2017	Update of section 4.8 of the SmPC with the adverse drug reaction frequencies to reflect overall exposure to eculizumab in clinical trials. Update of section 4.4 of the SmPC with warning and precautions on meningococcal vaccination timing as recommended by PRAC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (II/0086/G), which are available on the Agency's website**.
Tafinlar	All presentations	15/06/2017	Update of section 4.4 of the SmPC to add a new warning on colitis and gastrointestinal perforation, update of section 4.8 of the SmPC to include as new adverse drug reactions photosensitivity reaction with a common frequency, colitis and gastrointestinal perforation with a common frequency and myocarditis with a not known frequency. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/05/2017 (PSUSA/10084/201608), which are available on the European Commission website.**
Trajenta	All presentations	15/05/2017	Update of section 4.4 of the SmPC to add the adverse drug reaction bullous pemphigoid. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1140), which are available on the Agency's website**.

Tybost	All presentations	15/04/2017	To update the product information annexes with the PRAC adopted wording on interaction between cobicistat-containing products and corticosteroids. Section 4.5 of the SmPC and section 2 of the package leaflet have been updated with the PRAC adopted text. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/01/2017 (WS/1093), which are available on the Agency's website**.
Vfend	All presentations	15/04/2017	The package leaflet was amended to relocate allergic reaction or exaggerated immune response in the list of other side effects. **Parallel distributors must use the annexes dated 26/01/2017 (II/0121), which are available on the Agency's website**.
Victrelis	All presentations	15/06/2017	Update of sections 4.3 and 4.5 of the SmPC in order to add lurasidone in the list of contraindicated medications. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/04/2017 (II/0041), which are available on the Agency's website**.
Viekirax	All presentations	15/05/2017	Update of sections 4.4 and 4.5 of the SmPC to include a warning on the concomitant use of sirolimus and everolimus with dasabuvir and ombitasvir/paritaprevir/ritonavir and to update the information on the drug-drug interaction with sirolimus and everolimus. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2017 (WS/1079), which are available on the Agency's website**.

Vimpat	All presentations	15/05/2017	Update of section 4.2 of the SmPC in order to update the safety information regarding the use of lacosamide in patients with hepatic impairment. Update of section 4.8 to add a new adverse drug reaction (hepatic enzyme increased (> 2x ULN)) and update of section 4.9 regarding lacosamide overdose based on postmarketing reports. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/03/2017 (II/0066/G), which are available on the European Commission website.**
Vokanamet	All presentations	15/05/2017	Update of section 4.4 of the SmPC in order to update the safety information: the term 'and fatal' is added when describing diabetic ketoacidosis cases that have been reported. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 28/04/2017 (II/0026), which are available on the European Commission website**.
Zelboraf	All presentations	15/06/2017	Update of section 4.4 and 4.8 of the SmPC to add the adverse reactions Dupuytren's contracture and plantar fascial fibromatosis with common and uncommon frequency respectively. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/05/2017 (PSUSA/9329/201608), which are available on the Agency's website**.

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