15 May 2018
EMA/299291/2018
Inspections, Human Medicines Pharmacovigilance & Committees 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 a notification of change before implementation.

Name	EU number	Date of communication	Rationale
Adcetris	All presentations	15/04/2018	Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. **Parallel distributors must use the annexes dated 11/01/2018 (II/0049), which are available on the Agency's website**

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Apidra	All presentations	15/05/2018	To amend the SmPC sections 4.2, 4.4 and 6.6 and package leaflet sections 2 and 3 to implement the PRAC recommendation of potential increased risk of medication errors associated with withdrawing insulin from pre-filled pens and cartridges.. Also the MAH has updated pictures to reflect the revised packaging materials for Apidra SoloStar. The package leaflet and labelling are updated accordingly. **Parallel distributors must use the annexes dated 03/04/2018 (IB/0077), which are available on the Agency's website**
CellCept	All presentations	15/04/2018	This annex included several variations: update information on teratogenic effects and pregnancy as well as the contraception recommendations for male patients. Additional amendments have been made regarding use of contraception in women and pregnancy testing, to clarify the requirements. Update of section 4.4 of the SmPC in order to update the information on concomitant use of tacrolimus with CellCept and to provide recommendations on therapeutic drug monitoring for management of transplant patients, based on reviews of the medical literature and clinical treatment guidelines. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 12/03/2018 (T/0139), which are available on the Agency's website**
DuoTrav	All presentations	15/04/2018	Update of sections 4.8 of the SmPC in order to add "lid sulcus deepened" and "iris hyperpigmentation" as new adverse drug reactions with frequency not known and to upgrade the frequency of "skin hyperpigmentation (periocular)" from rare to uncommon based on the post-approval review of the safety data. In addition, section 4.8 of SmPC has been updated to align adverse drug reactions table for the travoprost monotherapy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/05/2017 (II/0052), which are available on the Agency's website**

Effentora	All presentations	15/03/2018	Update of sections 4.4 and 4.5 of the SmPC in order to add a warning on increased risk of depressant effects with the concomitant use of alcohol or other CNS depressants (e.g. opioids, sedatives or hypnotics, general anaesthetics, phenothiazine, tranquillisers, skeletal muscle relaxants, sedating antihistamine) with the possibility of a fatal outcome following a cumulative review on spontaneous reporting and literature review of this risk. 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**
Epivir	All presentations	15/03/2018	Update of section 4.2 of the SmPC of Epivir oral solution to recommend a 25% dose increase in children from 8 to 10 mg/kg/day, section 4.5 of the SmPC of both Epivir tablets and oral solution, and section 4.4 of the SmPC for Epivir oral solution only, to add information regarding the interaction between lamivudine and sorbitol based on the results of Study 204857. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 05/03/2018 (II/0104), which are available on the Agency's website**
Erelzi	All presentations	15/05/2018	Update of section 4.8 of the SmPC to update the frequency category of 7 ADRs currently listed and to split one ADR into 2. The description of the ADRs 'interstitial lung disease and 'autoimmune hepatitis' has also been amended. The MAH also took the opportunity to reformat the ADR listing in section 4.8 of the SmPC. Section 4.4 of the SmPC and the Package Leaflet are updated accordingly following the same changes for reference product Enbrel. In addition, the MAH updated wording of the sodium statement according to the "Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use'. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 28/03/2018 (IB/0006), which are available on the Agency's website**

Fiasp	All presentations	15/05/2018	Update of the RMP to upgrade the risk of mix-up between basal and bolus insulin from a potential to an important identified risk (RMP version 2.1); in addition, to update the secondary packaging material design and change colour of selected plastic components from yellow to red, consequently section 4.2 of the SmPC is being updated to no longer include the word “yellow” due to the new proposed colour coding of Fiasp. The package leaflet is updated accordingly. **Parallel distributors must use the annexes (when they start sourcing the new pen) dated 12/04/2018 (II/0003/G), which are available on the Agency’s website**
Firazyr	All presentations	15/05/2018	Update of section 4.8. of the SmPC to add “urticaria” as an adverse reaction with frequency “unknown” .The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/04/2018 (PSUSA/00001714/201707), which are available on the Agency’s website**
Fycompa	All presentations	15/05/2018	Update of section 4.4 and 4.8 of the SmPC to add a warning on severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), and to add the same adverse reaction with a frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/04/2018 (PSUSA/00009255/201707), which are available on the Agency’s website**

Herceptin	All presentations	15/05/2018	This annex combined two safety updates into this variation: to remove "pancreatitis" from the list of adverse drug reactions in section 4.8 of the SmPC and section 4 of the package leaflet. The MAH took this opportunity to make minor corrections to the annexes. E.g. to correct a,a-trehalose deihydrate and to further clarify the wording of side effects on abnormal development of lungs/kidney in neonates. Update the safety information administered in women with HER2 positive early breast cancer (EBC). Section 4.7 of the SmPC is also updated to reflect Herceptin has minor influence on the ability to drive or use machines. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 06/04/2018 (T/0142), which are available on the Agency's website**
Imnovid	All presentations	15/05/2018	Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to add new ADRs SJS, TEN and DRESS following a review of reports on severe skin reactions. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 23/04/2018 (II/0027), which are available on the European Commission website**
Invirase	All presentations	15/04/2018	Update of sections 4.2, 4.3, and 4.5 of the SmPC following an update to the company core data sheet in order to include a cross-reference to a new contraindication against switching from rilpivirine to invirase/ritonavir (section 4.2), to include lurasidone in the contraindications section (section 4.3) and to add information on additional interactions regarding lurasidone, rilpivirine, and tyrosine kinase inhibitors (section 4.5). The existing information regarding the interaction with alfuzosin has been updated to include a warning that co-administration may also cause potentially life-threatening cardiac arrhythmia. The existing information regarding interaction with medicines listed in the section 'neuroleptics' has been moved to the section 'antipsychotics' (section 4.5).The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/03/2018 (II/0122), which are available on the European Commission website (Please note that T/124 variation doesn't have the above side effects).**

Keytruda	All presentations	15/04/2018	Update of section 4.4 of the SmPC to add information regarding the risks of encephalitis, sarcoidosis and graft versus host disease (GVHD), including the occurrence of fatal GVHD events that have been reported with pembrolizumab in patients with a history of allogeneic Haematopoietic Stem Cell Transplantation (HSCT), and update of section 4.8 of the SmPC to add encephalitis as a 'rare' new ADR. Further, section 4.2 of the SmPC has been updated to include the recommendation to permanently discontinue pembrolizumab at the first occurrence of Grade 3 or 4 encephalitis and Grade 3 or 4 Guillain-Barré Syndrome (GBS). The package leaflet is updated accordingly as well as the Annex II; the information regarding educational material in the section 'additional risk minimisation measures'. **Parallel distributors must use the annexes dated 23/03/2018 (II/37/G), which are available on the European Commission website**
Kivexa	All presentations	15/03/2018	Update of section 4.5 of the SmPC to add information regarding the potential interaction between lamivudine and sorbitol based on the results of Study 204857. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 25/01/2018 (WS/1156), which are available on the Agency's website**
Kyprolis	All presentations	15/05/2018	Update of section 4.8 to include herpes zoster infection and confusional state as adverse drug reactions both with a frequency common. Section 4.2 is also aligned with this new information included in section 4.8. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/04/2018 (PSUSA/00010448/201707), which are available on the Agency's website**

Lynparza	All presentations	15/05/2018	Extension application to add a new pharmaceutical form associated with a new strength (100mg and 150 mg film-coated tablets) in the following extended indication: “as monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy.” The extension application is grouped with a Type II variation to align the PI for the currently authorised capsule licence with the safety updates proposed for the tablet formulation. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/05/2018 (X/16/G), which are available on the European Commission website**
Maviret	All presentations	15/05/2018	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update information on the use of Maviret in liver or kidney transplant patients, based on new clinical data from study M13-596 (MAGELLAN-2), a post-registrational Phase 3 study listed as a category 3 study in the RMP, which evaluated the efficacy and safety of the glecaprevir/pibrentasvir regimen in adult subjects with chronic hepatitis C virus genotypes 1-6 infection, who have received a liver or renal transplant. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/04/2018 (II/0004), which are available on the European Commission website**

NutropinAq	All presentations	15/03/2018	Update of sections 4.2, 4.4 and 4.5 of the SmPC to add new information on possible need for dose optimisation of somatropin in women and a warning about the concomitant use of oral oestrogen therapy and somatropin. The package leaflet is updated accordingly. Update of section 4.4 and 4.5 of the SmPC to add a warning on possible need for dose adjustment of glucocorticoid replacement therapy and to add information on interactions between somatropin and glucocorticoids. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/02/2018 (PSUSA/00002772/201703), which are available on the Agency's website**
Ocaliva	All presentations	15/04/2018	Update of section 4.2, 4.4 and 5.2 of the SmPC to add clear advice on recommended dosing in PBC patients with hepatic moderate and severe hepatic impairment, add a warning regarding dosing errors and to clarify advice on recommended dosing in patients with hepatic impairment. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 21/03/2018 (PSUSA/10555/201706), which are available on the European Commission website**
Omnitrope	All presentations	15/03/2018	Update of sections 4.2, 4.4 and 4.5 of the SmPC to add new information on possible need for dose optimisation of somatropin in women and a warning about the concomitant use of oral oestrogen therapy and somatropin. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 27/02/2018 (PSUSA/00002772/201703), which are available on the Agency's website**
Opdivo	All presentations	15/04/2018	Update of section 4.8 of the SmPC to add the adverse reaction tumour lysis syndrome with frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/03/2018 (PSUSA/10379/201707), which are available on the European Commission website**

Orkambi	All presentations	15/03/2018	Update of section 4.8 of the SmPC to add 'Blood creatine phosphokinase increased' with frequency 'common'. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 19/02/2018 (PSUSA/00010455/201705), which are available on the Agency's website**
Raxone	All presentations	15/05/2018	Update of SmPC section 4.5 to amend an existing warning in relation to CY3A4 substrates based on the final report of study SNT-I-017: An open-label study to assess the potential for pre-systemic inhibition of cytochrome P450 3A4 (CYP3A) by idebenone in healthy male subjects using midazolam as a substrate. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/03/2018 (II/0008), which are available on the Agency's website**
Remicade	All presentations	15/05/2018	Update section 4.4 of the SmPC and section 2 of the PIL to include a statement regarding the sodium content. Change the in use storage conditions and to extend the period of the storage of reconstituted product and inclusion of the diluted product in 0.9% NaCl infusion bags from 24 hours at 25°C to up to 28 days at 2 to 8°C prior to use for infusion and additional 24 hours at 25°C after removal from refrigerator. Furthermore the MAH took the opportunity to introduce an additional statement in section 6.6 of the SmPc to clarify that the storage of the preparation of Remicade concerns the infusion bags only. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 01/03/2018 (IB/0210/G), which are available on the Agency's website**
Reyataz	All presentations	15/04/2018	Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication with lurasidone to reflect this interaction based on literature data. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/02/2018 (WS/1292), which are available on the Agency's website**

Simponi	All presentations	15/04/2018	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on agranulocytosis and update neutropenia from uncommon to common based on new safety information in the company core data sheet (CCDS). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 22/03/2018 (IA/0076/G), which are available on the Agency's website**
Triumeq	All presentations	15/05/2018	Update of section 4.8 of the SmPC to add the new ADR 'anxiety' based on post-marketing and clinical trial data. Update of sections 4.5 and 5.2 of the SmPC based on new in vitro studies conducted for abacavir (ABC) and lamivudine (3TC). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 15/03/2018 (II/0047), which are available on the Agency's website**
Trulicity	All presentations	15/03/2018	Update of sections 4.2, 5.1 and 5.2 of the SmPC for Trulicity following completion of a Phase 3 study H9X-MCGBDX comparing the effect of once-weekly Trulicity with insulin glargine on glycaemic control over 52 weeks in patients with Type 2 Diabetes Mellitus and moderate or severe chronic kidney disease. In addition, the MAH took to opportunity to update the ATC code and to correct the "Instructions for use" in section 6.6 of the SmPC to make it consistent with instructions on "How to store Trulicity" in the package leaflet, which was also updated in section 2 'Warnings and precautions' to reflect the information in the "renal impairment" section 4.2 of the SmPC. **Parallel distributors must use the annexes dated 22/02/2018 (II/0022), which are available on the Agency's website**
Vectibix	All presentations	15/03/2018	Update of section 4.4 and section 4.8 of the SmPC and relevant sections of the PL to reflect a re-analysis of the safety information which pooled data from all the indications requiring a change in the overall incidence, severity, and seriousness of some of the currently labelled ADRs. **Parallel distributors must use the annexes dated 25/01/2018 (II/0086), which are available on the Agency's website**

Viekirax	All presentation	15/04/2018	Update of sections 4.3 and 4.5 of the SmPC to add disopyramide in the list of contraindicated medicines and in the list of medicines which interact with Viekirax. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 05/03/2018 (II/0039), which are available on the Agency's website**
Votrient	All presentation	15/04/2018	Update of section 4.8 of the SmPC in order to update the frequency of the adverse drug reaction 'infection' from uncommon to common. In addition, the marketing authorisation holder (MAH) took the opportunity to correct some discrepancies in sections 4.4, 4.5 and 4.8 of the SmPC. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/01/2018 (II/0043), which are available on the Agency's website**
Xgeva	All presentations	15/05/2018	Extension of indication to include prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with multiple myeloma and in adults with bone metastases from solid tumours for XGEVA; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. **Parallel distributors must use the annexes dated 29/03/2018 (II/0055), which are available on the European Commission website**
Zeffix	All presentations	15/03/2018	Update of section 4.5 of the SmPC to add information regarding a potential interaction with sorbitol-containing medicines. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 25/01/2018 (II/0069), which are available on the Agency's website**

Zydelig	All presentations	15/05/2018	Update of section 4.4 of the SPC to add a warning on reported cases of progressive multifocal leukoencephalopathy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 23/04/2018 (PSUSA/10303/201707), which are available on the European Commission website**

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