15 March 2018
EMA/98081/2018
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
Abilify	All presentations	15/01/2018	Update of sections 4.4 and 4.8 of the SmPC with further information about the risk of impulse control disorders, and section 4.8 of the SmPC to include the new ADRs 'impulse control disorders', 'binge eating', 'compulsive shopping' and 'poriomania' and to delete the ADR 'hyperglycaemia'. The package leaflet is updated accordingly. Further, the MAH has implemented minor editorial changes in section 6.1 of the SmPC, section 6 of the package leaflet and module 3.2.P.1 to include lactose as one of the components of the excipient vanilla flavour for Abilify orodispersible tablets. **Parallel distributors must use the annexes dated 26/10/2017 (II/0127), which are available on the Agency's website**

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Abilify Maintena	All presentations	15/01/2018	Update of sections 4.4 and 4.8 of the SmPC with further information about the risk of impulse control disorders, and section 4.8 of the SmPC to include the new ADRs 'impulse control disorders', 'binge eating', 'compulsive shopping' and 'poriomania'. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/10/2017 (II/0023), which are available on the Agency's website**
CellCept	All presentations	15/02/2018	Update of sections 4.4 and 4.5 of the SmPC of all pharmaceutical forms, in order to update information regarding potential interactions with antibiotics and other drugs interfering with glucuronidation pathway, based on a review of published literature. The package leaflet is updated accordingly. In addition, update of section 6.6 of the SmPC and section 3 of the package leaflet to improve the recommendations regarding safe handling of the powder for oral suspension formulation as well as other minor editorial changes. **Parallel distributors must use the annexes dated 23/11/2017 (II/0136), which are available on the Agency's website**
Cimzia	All presentations	15/02/2018	Update of section 4.8 of the SmPC to add the adverse reaction "worsening of symptoms of dermatomyositis" and to add the TNF-antagonist class adverse reactions: "Stevens-Johnson syndrome" and "erythema multiform » with a frequency "rare". The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/01/2018 (PSUSA/624/201703), which are available on the European Commission website**
Dexdor	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add polyuria with a frequency unknown. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/998/201703),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**
Esmya	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add the adverse reactions of drug hypersensitivity with a frequency uncommon and of angioedema with a frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/00009325/201702), which are available on the Agency's website**
Gilenya	All presentations	15/01/2018	Update of section 4.3 of the SmPC to include contra-indication for patients with underlying cardiac conditions, update of section 4.4 to add a warning on immunosuppressive effects and amend the existing warnings on infections and cutaneous neoplasms and update of section 4.8 of the SmPC to add the adverse reactions squamous cell carcinoma, Merkel cell carcinoma and to change the frequency of Kaposi's sarcoma from not known to very rare. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/10363/201701), which are available on the European Commission website**

Iclusig	All presentations	15/02/2018	Update of section 4.8 of the SmPC in order to include a paragraph regarding severe cutaneous adverse reactions (SCARs) reported in the post-marketing setting. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 07/12/2017 (II/0041), which are available on the Agency's website**
Imbruvica	All presentations	15/02/2018	Update of section 4.8 of the SmPC to add: 'panniculitis' with frequency 'uncommon'. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 09/02/2018 (PSUSA/10301/201705), which are available on the European Commission website**
Ixiaro	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add the adverse reaction 'Syncope' with a frequency 'rare'. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/01/2018 (PSUSA/00001801/201703), which are available on the Agency's website**
Jakavi	All presentations	15/01/2018	Update of section 4.4 of the SmPC to extend the existing warning on tuberculosis also to polycythaemiavera patients and of section 4.8 of the SmPC to add the adverse reaction pneumonia with a frequency common in myelofibrosis (MF) patients. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 01/12/2017 (PSUSA/10015/201702), which are available on the European Commission website**
Keytruda	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add pneumonia as an adverse drug reaction with a frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/ 10403/201703), 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	15/03/2018	Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information based on the second interim analysis of the overall survival data from study ENDEAVOR (study 20130398); this is a randomised, multicentre, open-label, phase 3 study of carfilzomib and dexamethasone compared to bortezomib with dexamethasone in patients with relapse multiple myeloma. Update of section 4.8 of the SmPC in order to revise the frequencies of certain adverse drug reactions based on the pooled data set including ENDEAVOR and 7 recently completed studies. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 25/01/2018 (II/0017/G), which are available on the Agency's website**
Lemtrada	All presentations	15/01/2018	Update of section 4.3, 4.4 and 4.8 of the SmPC to add a contraindication on patients with severe active infection until resolution, the adverse reaction listeria meningitis with a frequency of not known; to add the adverse reaction pneumonitis with a frequency uncommon; to add a warning on pneumonitis, and to revise an existing warning on listeriosis. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/10055/201703), which are available on the European Commission website**
Moventig	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add the adverse reaction Hypersensitivity with a frequency not known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/00010317/201703), which are available on the European Commission website**

Mysimba	All presentations	15/02/2018	Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the dosage recommendation and safety information for patients with moderate renal impairment. The proposed update removes the contraindication for patients with severe renal impairment, provides new information on the posology and additional warning that the maximum recommended daily dose for naltrexone / bupropion should be reduced for this patient population. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 26/01/2018 (II/0023), which are available on the Agency's website**
NeoRecormon	All presentations	15/02/2018	To update sections 4.4 and 4.8 of the SmPC and sections 2 and 4 of the package leaflet to implement the signal recommendations on 'Darbepoetin alfa; epoetin alfa; epoetin beta; epoetin theta; epoetin zeta; methoxy polyethylene glycol-epoetin beta – Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) **Parallel distributors must use the annexes dated 24/11/2017 (IAIN/0097), which are available on the Agency's website**
Neupro	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add the adverse reaction "diarrhoea" with a frequency not known. To replace the secondary packaging of the finished product: a folding cardboard carton is being replaced with a solid plastic box for Neupro EU/1/05/331/001-012 and EU/1/05/331/014. To change the time that time transdermal patch requires to be pressed against the skin from 20 s to 30 s. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 09/11/2017 (WS/1238/G), which are available on the Agency's website**

NutropinAq	All presentations	22/02/2018	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**
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**
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**
Revatio	All presentations	15/01/2018	Update of section 4.6 of the SmPC in order to revise the statement concerning the detection of sildenafil and its active metabolite in human milk and the potential for impact on the breastfed infant. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/10/2017 (II/0077), which are available on the Agency's website. The yearly update on EC website doesn't include this variation.**

Reyataz	All presentations	15/01/2018	Update of sections 4.4 and 4.8 of the SmPC to add a warning on chronic kidney disease observed in HIV infected patients during treatment with atazanavir (with or without ritonavir). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 11/12/2017 (WS/1193), which are available on the Agency's website**
Selincro	All presentations	15/02/2018	Update of section 4.4 of the SmPC to add a warning about the risk of suicidality in the target population. Update of section 4.8 of the SmPC to add the adverse drug reaction myalgia with frequency "unknown". The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA/10120/201702), which are available on the Agency's website**
Soliris	All presentations	15/02/2018	Update of sections 4.6 and 5.3 of the SmPC in order to update the safety information related to pregnancy, lactation and fertility following the review of data in PSUR 13 and 14. Annex II and the package leaflet are updated accordingly. **Parallel distributors must use the annexes dated 14/12/2017 (II/98), which are available on the Agency's website**
Taltz	All presentations	15/01/2018	Update of section 4.8 of the SmPC to add the adverse reaction "anaphylaxis" with a frequency rare and to modify the existing hypersensitivity warning in section 4.4. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/12/2017 (PSUSA /10493/201703), which are available on the European Commission website**
Toujeo	All presentations	15/02/2018	Update of sections 4.2, 4.4 and 6.6 of the SmPC in order to add a warning on the risk for medication error associated with pre-filled pens and cartridges presentations following the evaluation of a signal (EPITT 18893). The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/10/2017 (II/0100), 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**
Velphoro	All presentations	15/02/2018	Update of section 4.4 of the SmPC in order to remove a warning related to allergy to gluten. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/11/2017 (II/0012), which are available on the Agency's website**
Xalkori	All presentation	15/02/2018	Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the information about hepatic impairment based on the results of study A8081012 which evaluated the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/12/2017 (II/0050), which are available on the Agency's website**

Yervoy	All presentation	15/01/2018	Update of section 4.4 of the SmPC to add a warning on histiocytosis haematophagic and of section 4.8 of the SmPC to add 'pemphigoid' and 'histtiocytosis haematophagic' as new adverse drug reactions with a 'not known' frequency. The package leaflet is updated accordingly. In addition the MAH took the opportunity to include in section 4 of the package leaflet the standard statement about contacting your doctor in case of side effects to ensure consistency with the other frequency categories. **Parallel distributors must use the annexes dated 08/01/2018 (PSUSA/00009200/201703), which are available on the Agency's 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**
Zonegran	All presentations	15/02/2018	Update of section 4.4 and 4.6 to add information from a registry study on the risk of low birth weight and small for gestational age in infants exposed to zonisamide in utero and to update information regarding the need to counsel women of child-bearing potential on the risk of anti-epileptic drugs in pregnancy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 08/01/2018 (PSUSA/3152/201703), which are available on the Agency's website**

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