EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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.

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Name	EU number	Date of communication	Rationale
Actraphane	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website.**
Actrapid	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly.. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website.**
Adcetris	All presentations	15/01/2021	Update of section 4.8 of the SmPC to add infusion site extravasation (frequency unknown) for brentuximab vedotin monotherapy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/12/2020 (PSUSA/00010039/202002), which are available on the Agency's website**
Aldara	All presentations	15/01/2021	Update of sections 2 and 4 of the package leaflet to reflect the risk of exacerbation of autoimmune disorders. **Parallel distributors must use the annexes dated 09/12/2020 (PSUSA/00001729/202001), which are available on the Agency's website**

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BeneFIX	All presentations	15/01/2021	Update of section 4.2 of the SmPC to remove reference to the severity of the disease pertaining to the prophylaxis regimen. In addition, the product information was brought in line with the most recent QRD template version 10.1 and the MAH has taken the opportunity to include in section 4.4 of the SmPC an update related to the guideline on Excipients in the labelling and package leaflet of medicinal products for human use regarding the sodium content. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 27/11/2020 (N/0168), which are available on the Agency's website**
Betaferon	All presentations	15/01/2021	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on thrombotic microangiopathy by adding information about haemolytic anaemia and add haemolytic anaemia to the list of adverse drug reactions (ADRs) with frequency unknown based on the cumulative review of available data including case reports from post-marketing surveillance and scientific literature. The package leaflet has been updated accordingly **Parallel distributors must use the annexes dated 29/10/2020 (II/0130) which are available on the Agency's website**
Bevespi Aerosphere	All presentations	15/02/2021	Update of section 4.8 of the SmPC in order to add urinary tract infection' (UTI) to the list of adverse drug reactions (ADRs) with frequency common. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 17/09/2020 (II/0006) which are available on the Agency's website**
Biktarvy	All presentations	15/01/2021	Update of section 4.8 of the SmPC in order to add the Stevens-Johnson Syndrome (SJS) to the list of adverse drug reactions (ADRs) with frequency rare based on an internal cumulative safety review performed by the company and prompted by a spontaneous case report of a HIV patient who experienced SJS during treatment with Biktarvy. Update of section 4.8

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			of the SmPC to amend the wording of suicidal behaviour into suicidal ideation and suicide attempt in the light of the causal relationship between bictegravir / emtricitabine / tenofovir alafenamide and suicidal behaviour, with the frequency remaining uncommon. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 29/10/2020 (II/0034; this variation also includes the PSUSA/10695 /202002 scopes) which are available on the Agency's website**
Bosulif	All presentations	15/01/2021	Update of section 4.4 and 4.8 of the SmPC to add the adverse reaction photosensitivity reaction with a frequency common and a warning on the risk of photosensitivity. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/12/2020 (PSUSA/00010073/202003) which are available on the European Commission website**
Brintellix	All presentations	15/12/2020	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to reflect the outcomes of the paediatric clinical study 12710A (a paediatric efficacy and safety study in adolescent MDD patients) and the study 12708A (paediatric pharmacokinetics and tolerability study in children and adolescent patients with DSM-IV diagnosis of depressive and anxiety disorder). The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 18/11/2020 (II/0025) which are available on the European Commission website**
Busilvex	All presentations	15/12/2020	Update of section 4.5 of the SmPC regarding the interaction with deferasirox and iron chelating agents. Update of the SmPC section 5.2 with minor changes in the paediatric population PK parameters. In addition, the MAH took the opportunity to clarify statement on incompatibilities in sections 6.2 and 6.6 and to expand the incompatibility of the polycarbonates syringes with Busilvex to the incompatibility of any

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			infusion components containing polycarbonate with Busilvex. This change has been reflected on the subsection Instructions for use of the section 2" recommendations for safe handling" in the preparation guide of the package leaflet. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 01/10/2020 (II/0031) which are available on the Agency's website**
Bydureon	All presentations	15/02/2021	Update of section 4.8 of the SmPC to add delayed gastric emptying as a new ADR. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/00009147/202003) which are available on the European Commission website**
Byetta	All presentations	15/01/2021	Update of section 4.8 of the SmPC to add delayed gastric emptying as a new ADR. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/00009147/202003) which are available on the European Commission website**
Darzalex	All presentations	15/02/2021	Update of section 4.8 of the SmPC in order to include CMV infections as a new adverse drug reaction (ADR) with frequency common following a comprehensive, cross-program evaluation of all potential cases of treatment-emergent cytomegalovirus (CMV) infections with use of daratumumab. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 03/12/2020 (II/0041), which are available on the Agency's website**
Dovato	All presentations	15/12/2020	Update of section 4.6 of the SmPC to amend the new data regarding the transfer of DTG into breast milk. The package leaflet is updated accordingly where no wording on this effect yet exists. **Parallel distributors must use the annexes dated 18/11/2020 (PSUSA/00010075/202001), which are available on the Agency's website**

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Dupixent	All presentations	15/01/2021	Update of sections 4.4 and 4.8 of the SmPC to add the adverse reactions keratitis and ulcerative keratitis with a frequency uncommon in AD and keratitis with frequency rare for asthma are proposed. Respective warning is proposed to be added in the SmPC section 4.4. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/00010645/202003) which are available on the European Commission website**
Efficib	All presentations	15/01/2021	Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include data from the pooled analysis of paediatric studies P170 (sitagliptin/metformin) and P289 (sitagliptin/metformin extended release). The package leaflet is updated. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1898), which are available on the Agency's website**
Erleada	All presentations	15/01/2021	Update of section 4.8 of the SmPC in order to add toxic epidermal necrolysis and decreased appetite to the list of adverse drug reactions (ADRs) with frequency not known and very common respectively based on cumulative safety reviews; the package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 12/11/2020 (II/0007/G), which are available on the Agency's website**
Esbriet	All presentations	15/12/2020	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on drug-induced liver injury (DILI) subsequent to the latest PSUSA. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on hyponatraemia and to add hyponatraemia with a frequency uncommon to the list adverse reactions. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 16/11/2020 (II/0066/G), which are available on the Agency's website**
Extavia	All presentations	15/01/2021	Type II variation to update SmPC section 4.8 with the addition of haemolytic anaemia (HA) as an adverse drug reaction of unknown

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			frequency' based on cumulative review of available data including case reports from post-marketing surveillance and scientific literature. Section 4.4 of the SmPC and corresponding sections in the PL are updated with a precautionary statement, considering the importance of drug discontinuation for patients with thrombotic microangiopathy TMA/HA, to reflect the most recent post-marketing experience. **Parallel distributors must use the annexes dated 29/10/2020 (II/0103), which are available on the Agency's website**
Fiasp	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Gilenya	All presentations	15/01/2021	Update of section 4.4 of the SmPC, subsections infections and liver injury as well as Section 4.8 to add hepatobiliary disorders with a frequency not known: acute hepatic failure. In addition, the PL section 2 and section 4 should be updated accordingly. **Parallel distributors must use the annexes dated 14/12/2019 (PSUSA/00001393/202002), which are available on the Agency's website.**
Hexyon	All presentations	15/12/2020	Update of sections 4.4 and 5.1 of the SmPC in order to revise the warning regarding preterm infants and to add new information on immunogenicity in preterm infants and in infants born from women vaccinated during pregnancy, based on the final results from study A3L00053-EXT; this is an observational cohort study conducted by the Center for the Evaluation of Vaccination in Vaccine and

Name	EU number	Date of communication	Rationale
			Infectious Diseases Institute of University of Antwerp with DTaP-IPV-HB-PRP~T vaccine, aimed to describe the concentrations of IgG against the different antigens. The RMP version 12.0 has been submitted an updated accordingly, following revision 2 with consequential update to the safety concerns The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1792/G), which are available on the Agency's website.**
Imfinzi	All presentations	15/02/2021	Update of sections 4.4 and 4.8 of the SmPC in order to add immune thrombocytopenia to the list of adverse drug reactions (ADRs) with frequency (rare) following the MAH internal review; the package leaflet (PL) is updated accordingly. The MAH took the opportunity to correct information in the PL and to make editorial changes to the names of the manufacturer in Annex II and to units in Annex IIIA." **Parallel distributors must use the annexes dated 11/01/2021 (II/0023), which are available on the Agency's website**
Insulatard	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website.**
Invanz	All presentations	15/02/2021	Update of section 4.8 of the SmPC in order to add hypersensitivity vasculitis to the list of adverse drug reactions (ADRs) with frequency rare, based on post-marketing reports. The package leaflet is updated accordingly. **Parallel distributors must use the annexes**

Name	EU number	Date of communication	Rationale
			dated 03/12/2020 (II/0062), which are available on the Agency's website.
Jakavi	All presentations	15/01/2021	The product information should be updated adding adverse drug reactions pancytopenia (frequency - common) and HBV reactivation (frequency not known) and revising the warning on HBV reactivation in sections 4.8 and 4.4 of the SmPC, respectively. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/12/2020 (PSUSA/00010015/202002), which are available on the Agency's website.**
Janumet	All presentations	15/01/2021	Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include data from the pooled analysis of paediatric studies P170 (sitagliptin/metformin) and P289 (sitagliptin/metformin extended release). The package leaflet is updated **Parallel distributors must use the annexes dated 24/09/2020 (WS/1898), which are available on the Agency's website**
Keppra	All presentations	15/01/2021	Update of section 4.2 of the SmPC to recommend the same dosing for monotherapy and adjunctive therapy based on data from modelling and simulation project. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 17/12/2020 (WS/1664), which are available on the European Commission website**
Kinzalmono	All presentations	15/01/2021	Update section 4.4 of the SmPC and section 2 of the PL in order to implement the wording in compliance with the revised "Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), Revision 1 related to sorbitol and sodium content. Furthermore, MAH took this opportunity to implement QRD template version 10.1. Section 6 of the PL was updated to add 'K25' to povidone. **Parallel distributors must use the annexes dated 26/11/2020 (WS1950), which are available on the Agency's website**

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Kisplyx	All presentations	15/12/2020	Update of section 4.4 and 4.8 of the SmPC to add the adverse reaction osteonecrosis of the jaw with a frequency uncommon and a warning on the risk of osteonecrosis of the jaw. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/11/2020 (PSUSA/00010380/202002), which are available on the Agency's website**
Lenvima	All presentations	15/12/2020	Update of section 4.4 and 4.8 of the SmPC to add the adverse reaction osteonecrosis of the jaw with a frequency uncommon and a warning on the risk of osteonecrosis of the jaw. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 18/11/2020 (PSUSA/00010380/202002), which are available on the Agency's website**
Levemir	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Lorviqua	All presentations	15/01/2021	Update of sections 4.2, 4.4 and 4.8 to include the new term psychotic effects as an adverse drug reaction (ADR) based on the cumulative review of the data available through clinical databases and safety database. The package leaflet has been updated accordingly. **Parallel distributors must use the annexes dated 17/12/2020 (II/0008), which are available on the European Commission website**
Lyrica	All presentations	15/12/2020	Update of section 4.8 of the SmPC to add respiratory depression with frequency of not

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			known. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 20/11/2020 (PSUSA/00002511/202001), which are available on the Agency's website**
Mayzent	All presentations	15/01/2021	Addition of basal cell carcinoma in section 4.8 of the SmPC. The warning about cutaneous neoplasms is updated with the new information regarding the increase of the cases with long–term exposure. **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00010818/202003), which are available on the Agency's website**
Micardis	All presentations	15/01/2021	Update section 4.4 of the SmPC and section 2 of the PL in order to implement the wording in compliance with the revised "Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), Revision 1 related to sorbitol and sodium content. Section 6 of the PL was updated to add 'K25' to povidone. **Parallel distributors must use the annexes dated 26/11/2020 (WS1950), which are available on the Agency's website**
Mixtard	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Mysimba	All presentations	15/12/2020	Update of product information resulting from PRAC Assessment Report request in PSUSA/00010366/201909:

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			- Introduction of a warning concerning the interaction between Naltrexone/Bupropion and Digoxin in SmPC section 4.5 and related PL section. - Update of SmPC section 4.8 and related PL section on drug-induced lupus erythematosus with Naltrexone/Bupropion and its individual substances. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 01/10/2020 (II/0044/G), which are available on the Agency's website**
Neulasta	All presentations	15/02/2021	Sections 4.4 and 4.8 of the SmPC is updated to add a new warning on myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), and to add them in the list of adverse drug reactions (ADRs) with frequency uncommon. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/11/2020 (II/0113), which are available on the Agency's website**
NovoMix	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
NovoRapid	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help

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			preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Ocrevus	All presentations	15/01/2021	Update of sections 4.4 and 4.8 of the SmPC to add the adverse reaction late onset of neutropenia with a frequency not known. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/00010662/202003), which are available on the European Commission website**
Ofev	All presentations	15/01/2021	Update of section 4.4 of SmPC to add a warning on the risk of ischaemic colitis, and corresponding update of package leaflet. **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00010319/202004), which are available on the European Commission website**
Olumiant	All presentations	15/12/2020	Update of sections 4.8 of the SmPC to introduce the grouped term hypersensitivity, covering adverse events related to hypersensitivity, rash and urticaria, to the list of adverse drug reactions with a frequency uncommon. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 20/11/2020 (PSUSA/00010578/202002), which are available on the Agency's website**
Ovitrelle	All presentations	15/02/2021	Changes in sections 4.1, 4.2, 4.4 and 4.6 of the SmPC in order to update the terminology, in 4.3 to amend existing contraindications and in 4.8 to delete certain adverse drug reactions (ADRs) and add gastrointestinal ADRs with frequency common, with the aim to align the product information with similar text provided for other gonadotropin products. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 15/10/2020 (II/0081), which are available on the Agency's website**

Name	EU number	Date of communication	Rationale
Ozempic	All presentations	15/02/2021	Update of sections 4.2 and 5.1 of the SmPC in order to include information on the use of semaglutide once weekly in combination with a SGLT-2 inhibitor, based on the final results from the SUSTAIN 9 study (study NN9535-4269); this is a 30-week, randomised, double-blind, placebo-controlled phase 3 trial investigating the efficacy and safety of semaglutide as add-on to treatment with an SGLT-2 inhibitor ± metformin or sulphonylurea (SU) in subjects with T2D. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 03/12/2020 (II/0014), which are available on the Agency's website**
Praluent	All presentations	15/02/2021	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations, the undesirable effects section and pharmacokinetic and pharmacodynamic sections with information on paediatric population, based on final results from study EFC14660, a category 3 open-label study in the RMP, to evaluate the efficacy and safety of alirocumab in children and adolescents with homozygous familial hypercholesterolemia. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 14/12/2020 (IB/0060 which includes the II/0059 safety variation's scope), which are available on the Agency's website**
Prevenar 13	All presentations	15/12/2020	Update of section 4.8 of the SmPC to add the adverse reaction anaphylaxis with a frequency not known to the group of children > 5 years and adults. The MAH has taken the opportunity to move all events reported in the post marketing setting (not only anaphylaxis) from an age specific subsection (6 weeks to 5 years) into a subsection addressing all age ranges. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 25/11/2020 (PSUSA/00009263/202001), which are**

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			available on the European Commission website
Pritor	All presentations	15/01/2021	Update section 4.4 of the SmPC and section 2 of the PL in order to implement the wording in compliance with the revised "Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), Revision 1 related to sorbitol and sodium content. Section 6 of the PL was updated to add 'K25' to povidone. **Parallel distributors must use the annexes dated 26/11/2020 (WS/1950), which are available on the Agency's website**
Privigen	All presentations	15/12/2020	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to amend an existing warning on haemolytic anaemia and to update safety information based on final results from study IgPro10_5003 listed as a category 3 study in the RMP; this is an observational hospital-based cohort study in the US to evaluate Privigen use and haemolytic anaemia in adults and children and the Privigen safety profile in children with CIDP. : Update of sections 4.8 and 5.1 of the SmPC in order to update to the list of adverse drug reactions based on final results from study IgPro10_3004; this is a prospective open-label single-arm study of the pharmacokinetics and safety of intravenous IgPro10 in Japanese subjects with primary immunodeficiency. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 20/11/2020 (II/0161/G), which are available on the European Commission website**
Prolia	All presentations	15/12/2020	Updates to SmPC section 4.8 adding the adverse reactions hypersensitivity vasculitis with a frequency category of very rare and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with a frequency category of not known, and section 4.4 to introduce QRD traceability statement. The package leaflet is updated accordingly.

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			Parallel distributors must use the annexes dated 24/09/2020 (II/0085/G), which are available on the Agency's website
Protaphane	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Ranexa	All presentations	15/12/2020	Update of sections 4.8 of the SmPC in order to add myoclonus to the list of adverse drug reactions (ADRs) with frequency rare based on post-marketing data and update to section 4.9 based on review of the data regarding events of overdose. The package leaflet is updated accordingly**.** **Parallel distributors must use the annexes dated 08/10/2020 (II/0063), which are available on the Agency's website.**
Renvela	Powder for oral suspension presentations	15/01/2021	Update section 2 of the SmPC, labelling and section 2 of the PL for the powder for oral suspension presentations for Renvela and Sevelamer carbonate Winthrop to clarify the exact quantity and threshold of propylene glycol per product following the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) The **package leaflet** and **labelling** updated accordingly. **Parallel distributors must use the annexes dated 12/11/2020 (WS/1854), which are available on the Agency's website.**.
Replagal	All presentations	15/02/2021	Update of sections 4.8 and 4.4 of the Summary of Product Characteristics (SmPC) in order to update the list of adverse drug reactions (ADRs) information based on the final results

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			from study HGT-REP-081 a multicentre open-label treatment protocol to observe the safety of Replagal (agalsidase alfa) enzyme replacement therapy in Canadian patients with Fabry disease" and the safety information reported in clinical trials. In addition, the MAH took the opportunity to introduce editorial and QRD changes in sections throughout the Product Information according to the QRD templates and current guidelines, including new warnings related to sodium excipient and traceability of biological medicinal products. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 26/11/2020 (II/0106), which are available on the Agency's website.**
Ristfor	All presentations	15/12/2020	Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include data from the pooled analysis of paediatric studies P170 (sitagliptin/metformin) and P289 (sitagliptin/metformin extended release). The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 24/09/2020 (WS/1898), which are available on the Agency's website**
Rydapt	All presentations	15/01/2021	Update of sections 4.2 and 4.4 of the SmPC in order to change posology recommendations and add special warnings and precautions for use in paediatric population following the occurrence of severe dose limiting toxicities (DLTs) in the paediatric study CPKC412A2218 which is currently on clinical hold. The study is part of the agreed PIP (EMEA-000780-PIP01-09-M05) for which a request for modification was submitted on 20-Apr-2020. Section 5.1 of the SmPC and the package leaflet are updated accordingly. **Parallel distributors must use the annexes dated 22/01/2021 (II/0014), which are available on the Agency's website**
Ryzodeg	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and changed to highlight to

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			patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Sevelamer carbonate Winthrop	powder for oral suspension presentations	15/01/2021	Update section 2 of the SmPC, labelling and section 2 of the PL for the powder for oral suspension presentations for Renvela and Sevelamer carbonate Winthrop to clarify the exact quantity and threshold of propylene glycol per product following the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) The **package leaflet** and **labelling** updated accordingly. **Parallel distributors must use the annexes dated 12/11/2020 (WS/1854), which are available on the Agency's website.**
Stelara	All presentations	15/02/2021	Update of section 4.8 of the SmPC in order to add hypersensitivity vasculitis to the list of adverse drug reactions (ADRs) with frequency rare based on cumulative review from the literature and post-marketing reporting. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (YU which includes the II/0083 safety variation), which are available on the European Commission website**
Tasigna	All presentations	15/12/2020	Update of section 4.5 of the SmPC to add a warning on rhabdomyolysis caused by the drug-drug interaction with statins and update of section 4.8 to amend frequencies of the adverse reactions: cardiac failure, pneumonia, and renal failure. Update of section 4.8 undesirable effects" of the SmPC with facial paralysis with the frequency unknown. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 16/11/2020**

Name	EU number	Date of communication	Rationale
			(PSUSA/00002162/202001), which are available on the European Commission website
Tecfidera	All presentations	15/12/2020	Update of sections 4.3, 4.4 and 4.8 of the SmPC to reflect new available information on progressive multifocal leukoencephalopathy (PML) risk monitoring based on a cumulative review of PML cases in the setting of mild lymphopenia. The Package Leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/11/2020(II/0063) which are available on the Agency's website.**
Tenofovir disoproxil Mylan	All presentations	15/01/2021	Update of section 4.4 of the SmPC to amend the information on bone effects. Annex II and the Package leaflet are updated accordingly. Update of section 4.6 of SmPC to downgrade the current recommendation for breast-feeding for products indicated in the treatment of HBV. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/004049/00002892/202003), which are available on the European Commission website**
Tenofovir disoproxil Zentiva	All presentations	15/01/2021	Update of section 4.4 of the SmPC to amend the information on bone effects. Annex II and the Package leaflet are updated accordingly. Update of section 4.6 of SmPC to downgrade the current recommendation for breast-feeding for products indicated in the treatment of HBV. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 13/01/2021 (PSUSA/004049/00002892/202003), which are available on the European Commission website**
Tivicay	All presentations	15/12/2020	Update of section 4.6 of the SmPC to amend the new data regarding the transfer of DTG into breast milk. The package leaflet is updated accordingly where no wording on this effect yet exists. . **Parallel distributors must use the annexes dated 16/11/2020(PSUSA/00010075/202001)**

Name	EU number	Date of communication	Rationale
			which are available on the Agency's website.
Triumeq	All presentations	15/01/2021	Update of section 4.6 of the SmPC to amend the new data regarding the transfer of DTG into breast milk. The package leaflet is updated accordingly where no wording on this effect yet exists. **Parallel distributors must use the annexes dated 25/11/2020 (PSUSA/00010075/202001), which are available on the Agency's website.**
Truvada	All presentations	15/01/2021	Update of sections 4.4 and 5.1 of the SmPC to amend the information on bone effects. Annex II and the package leaflet are updated accordingly. **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00001210/202004), which are available on the European Commission website**
Velmetia	All presentations	15/12/2020	Update of the SmPC sections 4.2, 4.8, 5.1 and 5.2, to include data from the pooled analysis of paediatric studies P170 (sitagliptin/metformin) and P289 (sitagliptin/metformin extended release). In children and adolescents 10 to 17 years of age the product should not be used because of insufficient efficacy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS1898), which are available on the Agency's website.**
Viagra	All presentations	15/01/2021	Update section 4.4 of the SmPC and section 2 of the PL of the Product information in line with the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The MAH has proposed wording in the SmPC to correspond to the excipient guideline PIL wording relevant to patients with low sodium diets. The MAH has also taken the opportunity to correct an inaccuracy in the current Viagra 25 mg, 50 mg and 100 mg film-coated tablet SmPC related to the quantity of lactose calculated to be present in each tablet. The package leaflet is updated accordingly.

Name	EU number	Date of communication	Rationale
			Parallel distributors must use the annexes dated 12/11/2020 (WS/1948) which are available on the European Commission website
Vipdomet	All presentations	15/01/2021	Update of section 4.4 of the SmPC to add a warning on post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including alogliptin, and if bullous pemphigoid is suspected alogliptin should be discontinued. Update of section 4.8 of the SmPC to include the new adverse drug reactions bullous pemphigoid and interstitial nephritis (with frequency unknown). The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00010061/202004) which are available on the European Commission website**
Vipidia	All presentations	15/01/2021	Update of section 4.4 of the SmPC to add a warning on post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including alogliptin, and if bullous pemphigoid is suspected alogliptin should be discontinued. Update of section 4.8 of the SmPC to include the new adverse drug reactions bullous pemphigoid and interstitial nephritis (with frequency unknown). The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00010061/202004) which are available on the European Commission website**
Viread	All presentations	15/02/2021	Update of section 4.4 of the SmPC to amend the information on bone effects. Annex II and the package leaflet are updated accordingly. Update of section 4.6 of SmPC to downgrade the current recommendation for breast-feeding for products indicated in the treatment of HBV. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 14/01/2021 (PSUSA/00002892/202003), which are available on the Agency's website**

Name	EU number	Date of communication	Rationale
Xultophy	All presentations	15/12/2020	To implement the risk of cutaneous amyloidosis in sections 4.4 and 4.8 of the SmPC following a PRAC signal assessment (EPITT no. 19499). Sections 2 and 4 of the PL are updated accordingly and also changed to highlight to patients that the precautions they need to take (such as rotating the injection site) are important not only to help preventing cutaneous amyloidosis but also to help preventing lipodystrophy. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 24/09/2020 (WS/1901), which are available on the Agency's website**
Yervoy	All presentations	15/01/2021	Update of sections 4.4 and 4.8 of the SmPC to add solid organ transplant rejection with a frequency not known and to amend the information on the adverse reaction hemophagocytic lymphohistiocytosis. The package leaflet is updated accordingly **Parallel distributors must use the annexes dated 07/01/2021 (PSUSA/00009200/202003) which are available on the European Commission website**
Zonegran	All presentations	15/01/2021	Update of section 4.4 of the SmPC to add a warning on hyperammonaemia. The package leaflet is updated accordingly. **Parallel distributors must use the annexes dated 11/01/2021 (PSUSA/00003152/202003) which are available on the European Commission website**
Zyclara	All presentations	15/01/2021	Update of sections 2 and 4 of the Package Leaflet to reflect the risk of exacerbation of autoimmune disorders **Parallel distributors must use the annexes dated 14/12/2020 (PSUSA/00001729/202001), which are available on the Agency's website**

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