



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Symtuza

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification ¹ issued on	Commission Decision Issued ² / amended on	Product Information affected ³	Summary
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2024		PL	
IB/0051/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of	17/11/2023	n/a		

¹ Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.

² A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.

³ SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



	the AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/1599/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	14/04/2023	n/a		
II/0048	Submission of the final report from study TMC114FD2HTX3002 (DIAMOND). This is a phase 3, single-arm, open-label study to evaluate the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed-dose combination (FDC) regimen in newly diagnosed, antiretroviral treatment-naïve human immunodeficiency virus type 1 (HIV-1) infected subjects receiving care in a test and treat model of care. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	16/03/2023	n/a		

	of studies to the competent authority				
IB/0049	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/03/2023	15/06/2023	SmPC and PL	
WS/2342/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add 'crystal nephropathy' to the list of adverse drug reactions (ADRs) with frequency rare based on recent post-marketing data; the Package Leaflets are updated accordingly. In addition, sections 4.4 and 4.6 of the SmPC were updated to implement the recommendation of the CHMP to remove the disease information relating to sexual transmission of HIV and to amend the sections related to breast-feeding; the Package Leaflets are updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2022	15/06/2023	SmPC and PL	The key SmPC text resulting from this variation reads as follows - Section 4.6. Breast-feeding In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast feed. - Section 4.8. MedDRA system organ class Frequency category Adverse reaction Renal and urinary disorders Rare crystal nephropathy*§ § Adverse reaction identified in the post marketing setting. Per the guideline on Summary of Product Characteristics (Revision 2, September 2009), the frequency of this adverse reaction in the post marketing setting was determined using the "Rule of 3".
IAIN/0047/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	17/10/2022	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0045	Submission of the interim report from study GS-US-292-0106 listed as a category 3 study in the RMP. This is a Phase II/III, open-label study to evaluate of the pharmacokinetics, safety, tolerability, and antiviral activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir	01/09/2022	n/a		

	Alafenamide (E/C/F/TAF) single tablet regimen in HIV-1 infected antiretroviral treatment-naïve adolescents and virologically suppressed HIV-infected children. The RMP version 8.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/2290	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/07/2022	n/a		
R/0040	Renewal of the marketing authorisation.	24/03/2022	24/05/2022	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Symtuza in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
WS/2250	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to update the safety information based on final	19/05/2022	15/06/2023	SmPC and PL	SmPC Section 4.3. Concomitant administration of dabigatran has been deleted from contraindications. SmPC Section 4.5. Prezista

	results from study TMC114FD1HTX1002; this is an interventional phase 1, 2-Panel, Fixed-Sequence, Open-Label Single-Center Study to Assess the Effect of Single and Multiple Doses of Darunavir in Combination with Cobicistat or Ritonavir on the Pharmacokinetics of Single Dose Dabigatran Etxilate in Healthy Participants. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes in order to update the contact details of the local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				The use of boosted Prezista with a direct oral anticoagulant (DOAC) that is metabolised by CYP3A4 and transported by P gp is not recommended as this may lead to an increased bleeding risk. Darunavir/ritonavir: Clinical monitoring and/or dose reduction of the DOAC should be considered when a DOAC transported by P gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co administered with Prezista/rtv. Darunavir/cobicistat: Clinical monitoring and dose reduction is required when a DOAC transported by P gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co administered with Prezista/cobi. Rezolsta Co administration of Rezolsta with a direct oral anticoagulant (DOAC) that is metabolised by CYP3A4 and transported by P gp is not recommended as this may lead to an increased bleeding risk. Clinical monitoring and dose reduction is required when a DOAC transported by P gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co administered with Rezolsta. Symtuza Co administration of Symtuza with a direct oral anticoagulant (DOAC) that is metabolised by CYP3A4 and transported by P gp is not recommended as this may lead to an increased bleeding risk. Clinical monitoring and dose reduction is required when a DOAC transported by P gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co
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					administered with Symtuza. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10646 /202109	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	07/04/2022	n/a		PRAC Recommendation - maintenance
WS/2162	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/01/2022	24/05/2022	SmPC and PL	
WS/2179/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same	09/12/2021	n/a		

	pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
IA/0041/G	This was an application for a group of variations. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/12/2021	n/a		
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/09/2021	n/a		
WS/2035	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	02/09/2021	24/05/2022	SmPC and PL	SmPC new/harmonised text 4.5 Interaction with other medicinal products and other

	To update section 4.5 of the SmPC to provide guidance on drug-drug interaction between cutaneously-administered corticosteroids and boosted darunavir, darunavir/cobicistat and darunavir/cobicistat/ emtricitabine/tenofovir alafenamide, based on recent scientific literature publication. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet and to include minor editorial updates in the Product Information consisting of formatting, spelling and typo corrections. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				forms of interaction Interaction table [...] PREZISTA/REZOLSTA/SYMTUZA: Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone). REZOLSTA/SYMTUZA: Based on theoretical considerations DRV/COBI is expected to increase these corticosteroid plasma concentrations. (CYP3A inhibition) Concomitant use of boosted PREZISTA/REZOLSTA/SYMTUZA and corticosteroids (all routes of administration) that are metabolised by CYP3A may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone should be considered, particularly for long term use. [...] For more information, please refer to the Summary of Product Characteristics.
WS/2100/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	22/07/2021	n/a		

	1234/2008. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0035	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	03/05/2021	29/09/2021	SmPC and PL	
IB/0034/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or	28/04/2021	n/a		

	starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10646 /202009	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	09/04/2021	n/a		PRAC Recommendation - maintenance
IA/0033/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	22/02/2021	n/a		

	product - Minor changes to an approved test procedure				
IB/0029	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	20/01/2021	29/09/2021	SmPC, Labelling and PL	
IB/0031/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	18/01/2021	n/a		
IB/0028/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	26/11/2020	n/a		

	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0027	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/11/2020	n/a		
IG/1297/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	29/10/2020	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
WS/1883	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/09/2020	29/09/2021	SmPC and PL	
PSUSA/10646 /201909	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	17/04/2020	n/a		PRAC Recommendation - maintenance

IG/1205/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	07/02/2020	n/a		
WS/1753/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	30/01/2020	n/a		
II/0021/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/12/2019	n/a		

II/0020	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	12/12/2019	n/a		
PSUSA/10646 /201903	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	03/10/2019	n/a		PRAC Recommendation - maintenance
IB/0019/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters	08/07/2019	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.c.1.z - Change in immediate packaging of the AS - Other variation				
II/0017/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information based on week-96 results from studies TMC114FD2HTX3001 (AMBER) "A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF once daily fixed-dose combination regimen versus a regimen consisting of DRV/COBI FDC co-administered with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected subjects", and study TMC114IFD3013 (EMERALD) "A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects", both listed as category 3 studies in the RMP. The Package Leaflet is updated accordingly. The RMP version 5.2 (in version 2 of the RMP template) has also been submitted to reflect the study results and revise due dates for category 3 studies GS-US-311-1717 and GS-US-292-0109. In addition, the Marketing authorisation holder	29/05/2019	01/07/2019	SmPC and PL	The week 96 analysis of the ongoing, randomized, double-blind, active controlled two phase III studies (TMC114FD2HTX3001 (AMBER) and TMC114IFD3013 (EMERALD)) in HIV-1 infected, treatment-naïve and virologically suppressed patients is in line with the week 48 data, and similar conclusions could be drawn. Overall, the data confirmed the efficacy, demonstrating sustained antiviral efficacy, with an acceptable safety profile. Based on 96-week data sections 4.8 and 5.1 of the SmPC have been updated accordingly. The updated RMP version 5.2 was agreed.

	(MAH) took the opportunity to update section 4.2 of the SmPC and Package Leaflet to include advice in the event of vomiting in line with the approved Genvoya SmPC and make minor editorial changes in the SmPC; as well as to update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 of the SmPC of Prezista, Rezolsta and Symtuza to contra-indicate the concomitant use with dapoxetine, domperidone, ivabradine and naloxegol, as well as to update section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with dapoxetine, domperidone, fesoterodine, irinotecan, ivabradine, naloxegol and solifenacin based on approved product information. The Package Leaflets are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update of section 3 of the SmPC	28/03/2019	03/05/2019	SmPC, Labelling and PL	Darunavir used in combination with either ritonavir or cobicistat is an inhibitor of CYP3A, CYP2D6, and P-glycoprotein (P-gp). Co-administration of boosted darunavir with medicinal products primarily metabolized by CYP3A and/or transported by P-gp may result in increased systemic exposure to the co administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated. Based on these sections 4.3 and 4.5 of the SmPC of the Product Information for darunavir, darunavir/cobicistat fixed-dose combination, and darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination have been updated to provide further guidance for use in combination with ivabradine, naloxegol, dapoxetine, irinotecan, fesoterodine, solifenacin,

	of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling have been updated to reflect information on the in-use shelf-life in line with the approved Symtuza SmPC. Moreover, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the Package Leaflets of Prezista, Rezolsta and Symtuza have been updated to include information on the sodium excipient. Furthermore, the WSA took the opportunity to update the list of local representatives in the Package Leaflets of Prezista and Rezolsta in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				and domperidone, each of which are metabolized by CYP3A4 and/or CYP2D6, and/or transported by P-gp. This guidance is aligned with the recommendations in the Product Information of those respective products considering the mechanistic basis of these interactions.
PSUSA/10646 /201809	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	11/04/2019	n/a		PRAC Recommendation - maintenance
WS/1503/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing	28/02/2019	n/a		

process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
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	specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.III.1.b.1 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for an AS from a new or an already approved manufacturer				
IB/0014	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	17/12/2018	n/a		
WS/1474/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 of the SmPC of Prezista, Rezolsta and Symtuza to contra-indicate the concomitant use with dabigatran, as well as to update section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with edoxaban and dabigatran. Update of section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with Hepatitis C virus direct-acting antivirals: glecaprevir/pibrentasvir. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	18/10/2018	20/11/2018	SmPC and PL	Concomitant administration of administration of darunavir when used in combination with low-dose of ritonavir or cobicistat, may lead to a substantial increase in exposure to dabigatran. Therefore, concomitant treatment with dabigatran is contraindicated. Edoxaban is a substrate of P glycoprotein, which can be inhibited by darunavir when used in combination with low-dose of ritonavir or cobicistat, resulting in its increased plasma levels which may lead to an increased risk of bleeding. Therefore, the co-administration is not recommended. Glecaprevir/pibrentasvir are substrates for P glycoprotein and/or BCRP. Glecaprevir is also a substrate of OATP1B1/3. Darunavir when used in combination with low-dose ritonavir or cobicistat may increase the exposure to glecaprevir and pibrentasvir (P glycoprotein, BCRP and/or OATP1B1/3 inhibition). Therefore, the co-administration is not recommended. Based on these theoretical considerations, the products

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				information of Prezista, Rezolsta and Symtuza are updated
IG/0980	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	03/05/2019	SmPC and PL	
PSUSA/10646 /201803	Periodic Safety Update EU Single assessment - darunavir / cobicistat / emtricitabine / tenofovir alafenamide	04/10/2018	n/a		PRAC Recommendation - maintenance
IB/0010/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch	21/09/2018	n/a		

	size B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)				
WS/1312	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4, 4.6 and 5.2 of the SmPCs for Prezista, Rezolsta and Symtuva to reflect the data of the category 3 study TMC114HIV3015 in HIV-1 infected pregnant women. The PL of Prezista, Rezosta and Symtuza are also updated accordingly. Updated RMPs (version 25.6 for Prezista, 4.6 for Rezolsta and 4.0 for Symtuza) are agreed accordingly. In addition, the MAH took the opportunity to implement the template version 2 for the Prezista and Rezolsta RMPs, removal of the fulfilled category 4 DAD study from the Prezista and Rezolsta RMPs,	31/05/2018	06/07/2018	SmPC and PL	The pharmacokinetic, efficacy and safety data from the darunavir (DRV)/cobicistat (COBI) arm of the Phase 3b Study TMC114HIV3015 in human immunodeficiency virus type 1 (HIV-1) infected pregnant women were presented and assessed. In total, 7 subjects were enrolled to the DRV/COBI arm, of which 6 (85.7%) subjects completed the study. The pharmacokinetic data demonstrate that mean exposure (AUC) of darunavir boosted with cobicistat was 56% and 50% lower during the 2nd and 3rd trimester of pregnancy, respectively, compared with 6 to 12 weeks postpartum. Mean darunavir Cmin concentrations were ~90% lower during the 2nd and 3rd trimester of pregnancy as compared to postpartum. Mean darunavir Cmin concentrations of 168-184 ng/ml for DRV/COBI during the 2nd and 3rd trimester of pregnancy were below the previously targeted 550 ng/ml (EPAR Prezista) and considerably lower than the mean darunavir Cmin concentrations of 1100-1200 ng/ml for the DRV/RTV arm of

	removal of observational study on growth in children and 'growth abnormalities in the paediatric population' as important potential risk in the Prezista RMP and addition of the missing information 'Safety in patients with cardiac conduction disorders' in the Rezolsta RMP (alignment with Tybost RMP) and removal of 'Use in pregnant and breast-feeding women' as missing information, removal of the PANNA study (RMP cat 3), and update of the clinical trial and post-marketing sections with most recent data up to DLP of 20 October 2017. Correction of data for TMC114HIV3015 (DRV/rtv arm) in section 5.1 of the SmPC were also implemented. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				study TMC114HIV3015. Exposure of cobicistat was 63% and 49% lower during the 2nd and 3rd trimester of pregnancy, respectively, compared with 6 to 12 weeks postpartum. As the exposure of cobicistat is reduced in pregnant women, probably the boosting by cobicistat is no longer maximal. In view of the observed low exposure values of darunavir/cobicistat during pregnancy, the CHMP agreed to strongly recommend against the use of darunavir/cobicistat during pregnancy. This should apply to pregnant women who are already on a DRV/COBI containing regimen, as well as to those who are naïve to DRV/COBI.
IG/0941/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size	05/06/2018	n/a		

	ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size				
II/0003/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/04/2018	06/07/2018	SmPC, Labelling and PL	
II/0002/G	This was an application for a group of variations. C.I.13 - type II to submit the results of the study GS-US-311-1089 "A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV 1 Positive Subjects who are Virologically Suppressed on Regimens containing FTC/TDF". The RMP version 1.3 has been updated to reflect the completion of the study. C.I.11.z - type II to update the RMP version 1.3 to remove pancreatitis, convulsion, and cardiac conduction abnormalities as risks in the RMP in alignment with the RMP for Prezista and Rezolsta. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered	08/03/2018	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0007	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/02/2018	n/a		
WS/1300/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the Prezista, Rezolsta and Symtuza SmPC to reflect the drug-drug interaction results of the pharmacology studies GS-US-216-1008 (DDI between DRV+COBI and HMG CoA reductase inhibitors rosuvastatin and/or atorvastatin) and GS-US-216-4032 (DDI between DRV+COBI and the hormonal contraceptive medication drospirenone/ethinyl estradiol). Update of section 4.9 of the Prezista, Rezolsta and Symtuza SmPC to remove the recommendations regarding emesis and administration of activated charcoal in case of overdose. In addition, the Worksharing applicant (WSA) took the opportunity to harmonize between Prezista, Rezolsta and Symtuza the DDI information with emtricitabine/tenofovir alafenamide, clonazepam, isavuconazole, lomitapide, fentanyl, oxycodone, tramadol and lorazepam. The MAH also took the opportunity to align the in-	15/02/2018	06/07/2018	SmPC, Labelling and PL	Rosuvastatin AUCinf, AUClast, and Cmax were 1.9-, 2.3-, and 3.8-fold higher, respectively, following co-administration of DRV+COBI (800 mg + 150 mg q.d.) plus rosuvastatin (10 mg) compared to rosuvastatin alone (study GS-US-216-1008). Atorvastatin AUCinf, AUClast, and Cmax were 3.9-, 4.3-, and 4.2-fold higher, respectively, following co-administration of DRV+COBI (800 mg + 150 mg q.d.) plus atorvastatin (10 mg) compared to atorvastatin alone. Following co-administration of DRV+COBI (800 mg + 150 mg q.d.) plus drospirenone/ethinylestradiol (3/0.2mg) compared to drospirenone/ethinylestradiol alone, drospirenone AUCinf and AUClast were 1.6- and 1.5-fold higher, respectively, and ethinyl estradiol AUCinf and AUClast were 30% lower (study GS-US-216-4032). The Product Information of Prezista, Rezolsta and Symtuza were updated with the relevant data and information of these Drug-Drug interactions studies. In addition, the DDI information was harmonized between the 3 products and section 4.9 was updated to remove the recommendation regarding emesis and charcoal administration.

	use shelf-life in label and PL with the SmPC. The PL is updated accordingly and the local representatives' details are updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0006	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/01/2018	n/a		
IB/0001/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/10/2017	06/07/2018	SmPC, Labelling and PL	