Rezolsta

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
R/0031	Renewal of the marketing authorisation.	29/05/2019	31/07/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Rezolsta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0032/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	15/07/2019	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).

	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.7 - Administrative change - Deletion of manufacturing sites 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.c.1.z - Change in immediate packaging of the AS - Other variation				
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 of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling	28/03/2019	06/05/2019	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, and domperidone, each of which are metabolized by CYP3A4

	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/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.
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 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	28/02/2019	n/a		

	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 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				

PSUSA/10315 /201805	Periodic Safety Update EU Single assessment - darunavir / cobicistat	29/11/2018	n/a		PRAC Recommendation - maintenance
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 data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	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 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	06/05/2019	SmPC and PL	
WS/1312	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	31/05/2018	29/06/2018	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

	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, 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				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 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 ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	05/06/2018	n/a		
WS/1355	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/03/2018	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	15/02/2018	29/06/2018	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.)

	(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 emtricibine/tenofovir alafenamide, clonazepam, isavuconazole, lomitapide, fentanyl, oxycodone, tramadol and lorazepam. The MAH also took the opportunity to align the in-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				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, drosperidone 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.

PSUSA/10315 /201705	Periodic Safety Update EU Single assessment - darunavir / cobicistat	30/11/2017	n/a		PRAC Recommendation - maintenance
PSUSA/10315 /201611	Periodic Safety Update EU Single assessment - darunavir / cobicistat	09/06/2017	n/a		PRAC Recommendation - maintenance
WS/1089/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. Submission of the final report from Study GS-US-236-0140 listed as a category 3 study in the RMP. This is a randomized, open-label, phase 4 study evaluating the renal effect of Elvitegravir/ Cobicistat/ Emtricitabine/Tenofovir DF or other Tenofovir DF-containing Regimens (Ritonavir-boosted Atazanavir plus Emtricitabine /Tenofovir DF or Efavirenz /Emtricitabine/Tenofovir DF) compared to Ritonavir-boosted Atazanavir plus Abacavir/ Lamivudine in Antiretroviral Treatment-naïve HIV-1 Infected Adults with eGFR ≥70 mL/min. The RMP has been updated accordingly and the important potential risks of renal toxicity removed. Based on cumulative review of the available data, the Prezista and Rezolsta RMPs are updated to remove the important risks of 'pancreatis', 'convulsions' and 'cardiac conduction abnormalities' . The MAH took the opportunity of this procedure to include the Annex 7 in the Prezista RMP. The consolidated updated RMPs version 25.1 for	23/03/2017	n/a		

	Prezista and version 4.2 for Rezolsta are agreed. 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				
WS/1059	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Updated RMP (Prezista RMP version 25.1 and Rezolsta version 4.2) in order to delete the cat 3 study TMC114HIV3015 in HIV-1 infected pregnant women and replace the commitment by the assessment of the pharmacokinetics data in HIV-1 pregnant women. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	23/03/2017	n/a		
IG/0783	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	14/03/2017	n/a		

WS/1107/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 sections 4.3 and 4.5 of the SmPC with contra-indication and information of drug-drug interactions of boosted darunavir with elbasvir/grazoprevir (Zepatier) and with lurasidone (Latuda). The PL was updated accordingly. Update of section 4.5 of the Prezista SmPC regarding the drug-drug interaction of boosted darunavir with corticosteroids in line with the PRAC Recommendation for Rezolsta. In addition, the MAH took the opportunity of this variation, for both products, to add information regarding alfuzosin in section 4.5 in line with section 3, to add inhibition of CYP2D6 for the alfa 1 adrenoreceptor antagonist and to correct the frequency of the adverse event osteonecrosis. Section 4.5 of Prezista was also updated to align information between the different formulations and with Rezolsta. An error was correct in section 5.2. The MAH also took the opportunity to update the Product Information with the lasts QRD templates version 9.1 and 10. The contact of the Dutch local representative in the PL was updated. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/02/2017	08/02/2018	SmPC, Annex II, Labelling and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0016/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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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.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.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	06/01/2017	n/a		

PSUSA/10315 /201605	Periodic Safety Update EU Single assessment - darunavir / cobicistat	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0014	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2016	26/01/2017	SmPC and PL	
WS/0955	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	n/a		
PSUSA/10315 /201511	Periodic Safety Update EU Single assessment - darunavir / cobicistat	09/06/2016	n/a		PRAC Recommendation - maintenance
II/0003	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	n/a		
N/0011	Update of the package leaflet with revised contact details of local representative for Estonia, Lithuania, Latvia, Romania and Sweden. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/04/2016	26/01/2017	PL	
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/04/2016	n/a		

WS/0872	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	28/01/2016	26/01/2017	SmPC and PL	
PSUSA/10315 /201505	Periodic Safety Update EU Single assessment - darunavir / cobicistat	03/12/2015	n/a		PRAC Recommendation - maintenance
IA/0008	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/11/2015	n/a		
IB/0005/G	This was an application for a group of variations. 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 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	08/07/2015	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0004/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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/06/2015	n/a		
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
IB/0001/G	This was an application for a group of variations. 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.4 - Administrative change - Change in the name	29/01/2015	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.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 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				