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
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	10/11/2022		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

[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).

	‘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				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/0050/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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	10/10/2022	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 A.7 - Administrative change - Deletion of manufacturing sites 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				
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		
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	19/05/2022	20/10/2022	SmPC and PL	SmPC Section 4.3. Concomitant administration of dabigatran has been deleted from contraindications. SmPC Section 4.5.

	to update the safety information based on final 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 Etexilate 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				Prezista 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 administered with Symtuza. For more information, please refer to the Summary of Product Characteristics.
IA/0047	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/03/2022	n/a		
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	20/10/2022	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	09/12/2021	n/a		

	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.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				
WS/2035	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.	02/09/2021	20/10/2022	SmPC and PL	SmPC new/harmonised text 4.5 Interaction with other medicinal products and other 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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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 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	22/07/2021	n/a		

IB/0042/G	This was an application for a group of variations. 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 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.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	22/04/2021	n/a		
PSUSA/10315	Periodic Safety Update EU Single assessment -	14/01/2021	n/a		PRAC Recommendation - maintenance

/202005	darunavir / cobicistat				
IG/1297/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.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	29/10/2020	n/a		
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	03/09/2020	23/09/2021	SmPC and PL	

	data				
II/0033	To extend the approved therapeutic indication of Rezolsta to include the adolescent population (aged 12 years old and older with body weight at least 40 kg). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 6.0 has also been submitted. The RMP of the product has been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns. In addition, in order to align the PI with recommendations for other HIV products, the MAH has also taken the opportunity to update section 4.2 of the SmPC with regards to the administration of Rezolsta in case of vomiting. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/01/2020	09/03/2020	SmPC and PL	Please refer to Scientific Discussion: Rezolsta-H-C-002819-II-33

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		
PSUSA/10315 /201905	Periodic Safety Update EU Single assessment - darunavir / cobicistat	28/11/2019	n/a		PRAC Recommendation - maintenance
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	09/03/2020	SmPC and PL	

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 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	15/07/2019	n/a		
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	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

	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 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				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 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	28/02/2019	n/a		

	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 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.	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

	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				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. 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	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 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

	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				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	05/06/2018	n/a		

	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				
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 (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	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.) 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).

	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				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 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	23/03/2017	n/a		

	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.	23/02/2017	08/02/2018	SmPC, Annex II, Labelling and PL	

	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 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	Periodic Safety Update EU Single assessment -	01/12/2016	n/a		PRAC Recommendation - maintenance

/201605	darunavir / cobicistat				
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	29/01/2015	n/a		

	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.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				