Prezista

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/0123	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2024		PL	
IG/1599/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	14/04/2023	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).

	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.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition				
IB/0120/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished 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	23/11/2022	n/a		
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.	10/11/2022	15/11/2023	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*§

	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				§ 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".
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		
IA/0118	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	20/05/2022	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 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	19/05/2022	15/09/2022	SmPC and PL	SmPC Section 4.3. Concomitant administration of dabigatran has been deleted from contraindications. SmPC Section 4.5. 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

	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				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.

IB/0115	B.II.b.3.f - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process of an aqueous oral suspension	22/02/2022	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	15/09/2022	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 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	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				
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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/09/2021	15/09/2022	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 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		
PSUSA/934/202012	Periodic Safety Update EU Single assessment - darunavir	08/07/2021	n/a		PRAC Recommendation - maintenance
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	
II/0107	Extension of indication for Prezista (darunavir) in combination with cobicistat for the treatment of HIV-1 infection in adolescents aged 12 years and older with body weight at least 40 kg. As a consequence,	23/07/2020	28/08/2020	SmPC and PL	Please refer to Scientific Discussion 'Prezista-H-C-000707-II-0107'.

	sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and section 3 of the Package Leaflet are being updated accordingly. The updated RMP version 27.2 has been submitted. In addition, in order to align the SmPC with recommendations for other HIV products, the MAH has also taken the opportunity to update section 4.2 throughout with regards to the administration of Prezista in case of vomiting. The MAH has also implemented some editorial changes in Annex II and IIIA. The package leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0106	C.I.7.b - Deletion of - a strength	15/05/2020	28/08/2020	SmPC, Labelling and PL	
IB/0104	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)	25/02/2020	28/08/2020	SmPC and PL	
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	07/02/2020	n/a		

	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/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		
IB/0102/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	16/07/2019	n/a		

	- 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 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	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, 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.

	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				
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 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)	28/02/2019	n/a		

	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				
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	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-

	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				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	03/05/2019	SmPC and PL	
PSUSA/934/201712	Periodic Safety Update EU Single assessment - darunavir	12/07/2018	n/a		PRAC Recommendation - maintenance
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.	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

	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				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.
IB/0097	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/06/2018	n/a		

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	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,

	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 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				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). 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.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0092/G	This was an application for a group of variations. 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 B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	11/01/2018	n/a		
IB/0090/G	This was an application for a group of variations. 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 B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	13/12/2017	n/a		
IB/0089	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/09/2017	n/a		

II/0083/G	This was an application for a group of variations. B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients B.II.a.4.a - Change in coating weight of oral dosage forms or change in weight of capsule shells - Solid oral pharmaceutical forms 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.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/06/2017	05/02/2018	SmPC and PL	
IA/0088	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)	01/06/2017	n/a		

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	23/03/2017	n/a		

	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.	23/02/2017	05/02/2018	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/0082/G	This was an application for a group of variations. 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 B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	17/11/2016	n/a		
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		
N/0080	Update of the package leaflet with revised contact details of the local representatives 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	05/02/2018	PL	
II/0078	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	26/02/2016	SmPC and PL	
II/0075	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	26/02/2016	SmPC and PL	
PSUSA/934/201412	Periodic Safety Update EU Single assessment - darunavir	09/07/2015	n/a		PRAC Recommendation - maintenance
IB/0076/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	02/07/2015	n/a		
IAIN/0077	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	24/06/2015	n/a		
IB/0071	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	15/04/2015	n/a		

	authorisation, including the RMP - Other variation				
IB/0070/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.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	20/03/2015	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		
IG/0526/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/03/2015	26/02/2016	Annex II and PL	
IB/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/02/2015	n/a		
II/0064	Update of the SmPC (sections 4.1 [75/150/300/600 mg tablets)] 4.2, 4.4 and 5.2) with an extension of	25/09/2014	30/10/2014	SmPC and PL	With this type II variation, the MAH requests an extension of the indication to:

	indication to use darunavir once daily in children aged 3 to 12 years ≥ 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance-associated mutations (DRV RAMs). This proposed change is based on the data from a 2 week once daily substudy of the Phase 2 study TMC114 C228 and results from model-based pharmacokinetic simulations. The Package Leaflet has been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				"Darunavir administered once daily in combination with low-dose rtv and with other ARV agents, in paediatric subjects aged 3 to <12 years and weighing ≥15 kg who are 1) treatment-naive or 2) treatment experienced with no DRV RAMs, plasma HIV-I RNA <100,000 copies/ml, and CD4+ cell count >100x106 cells/l." As stated in the CHMP guideline on the clinical development of medicinal products for the treatment of HIVinfection (Doc. Ref. EMEA/CPMP/EWP/633/02), provided that reliable pharmacokinetic data support robust dose recommendations, an extrapolation of efficacy data obtained in adults to children may be accepted. Exposures with the once daily dose of 600/100 mg DRV/rtv as recommended for treatment-naïve children weighing ≥15kg and <30kg are similar to the once daily regimen of 800/100 mg DRV/rtv in adults and comparable to exposures with twice daily dosing as recommended in paediatric and adult patients. As such, safety and efficacy can be extrapolated. There seems no indication that higher exposures (i.e. ≥10,000 to <15,000 ng/mL, or ≥15,000 ng/mL) would result in an increase in adverse events, increased toxicity. The safety data in the claimed paediatric indication do not give rise to any new clinically relevant findings compared with the known DRV/rtv safety profile in HIV-1 infected adults. Lipid abnormalities and growth impairment were identified as potential risks related to the use of darunavir in treatment-naïve HIV-1 infected adolescents and adequate measures have been put in place to monitor those.
II/0063	Update of sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7,	25/09/2014	30/10/2014	SmPC, Annex	Refer to the EPAR assessment report.

	4.8, 5.1 and 5.2 of the SmPC for the 100mg/ml oral suspension and the 400mg, 800mg film-coated tablets with information on the use of darunavir with cobicistat as pharmacokinetic enhancer. Consequential changes have been introduced in the SmPC of all formulations and also in the Package Leaflet (for 100mg/ml, 400 mg and 800 mg film-coated tablets). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The manufacturer's address is also corrected in the PL. Furthermore, there is an update of the Annex II with a correction to the address of one of the manufacturers responsible for batch release. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II and PL	
II/0067/G	This was an application for a group of variations. Update of sections 4.3 and 4.5 of the SmPC with information on CYP3A/CYP2D6 mechanism based interactions. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in sections 4.3, 4.4, 4.5 and 9 of the SmPC, to update section 5.1 of the	25/09/2014	30/10/2014	SmPC and PL	Based on drug-drug interaction information that became recently available regarding the metabolic characteristics of the respective drugs or their effect on metabolising enzymes involved in the darunavir metabolism, Prezista Product Information has been updated with regards to CYP3A and CYP2D6 mechanism based interactions. These updates are primarily based on existing literature data and on data from a completed pharmacokinetic study and are aligned with the product information of the co-administered

	SmPC regarding the decreased susceptibility of emerging viruses and to update the list of 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				drugs.
PSUV/0066	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IA/0068	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	15/05/2014	n/a		
WS/0507	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Worksharing procedure for Prezista, Intelence and Edurant to update section 4.4 of the SmPC with a revised wording on the risk of transmission. The PL has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/03/2014	30/10/2014	SmPC and PL	During recent years conclusive evidence has been collected which shows that the risk for HIV patients, who are well treated, to sexually transmit HIV to their partner is exceedingly low. A position statement on the use of antiretroviral therapy to reduce HIV transmission was published by the British HIV Association (BHIVA) in January 2013. As a consequence, the recommendations for post-exposure prophylaxis have also been changed in recently updated HIV treatment guidelines. For example, the 2013 BHIVA guideline does not generally recommend post-exposure prophylaxis (PEP) after exposure from a patient with well treated HIV. Based on these data, the wording on the risk of transmission for HIV products was revised to reflect the current scientific knowledge. While effective suppression with antiretroviral therapy has been proven to

					substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.
IB/0062/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	04/02/2014	n/a		
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/10/2013	18/11/2013	SmPC and PL	Update the sections 4.3 and 4.5 of the SmPC for darunavir in line with the PRAC Recommendations. The PL has been updated accordingly. Furthermore, the list of local representatives has been updated for Czech Republic, Hungary, Norway, Portugal, Iceland and Romania.
PSUV/0059	Periodic Safety Update	25/07/2013	19/09/2013	SmPC and PL	Please refer to: H-707-PSUV-59 "Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation."
R/0055	Renewal of the marketing authorisation.	25/07/2013	19/09/2013	SmPC, Annex II and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Prezista continues to be favourable.

					The CHMP is of the opinion that the renewal can be granted with unlimited validity. Finally, the CHMP recommends that the MAH will continue to submit yearly PSURs. The next PSUR submission is due by 03/03/2014 in accordance with the published EURD list.
II/0054	Update of the sections 4.1, 4.2, 4.8, 5.1 and 5.2 of SmPC of the 100mg/ml oral suspension, the 400mg and the 800mg film-coated tablets formulations with an indication for use of DRV/rtv once daily regimen in paediatric patients 12 to 17 years of age and weighing at least 40 kilograms who are antiretroviral treatment naïve or with prior exposure to antiretroviral medicinal products but without DRV RAMs and who have plasma HIV 1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. As a consequence of these changes, sections 4.2, 4.8, 5.1 and 5.2 of SmPC of the 75mg, 150mg, 300mg and the 600mg film-coated tablets formulations have been updated. Editorial changes were made in the section 4.5 of all the presentations. The PL is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2013	19/09/2013	SmPC and PL	Please refer to: H-707-II-54
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
WS/0396	This was an application for a variation following a worksharing procedure according to Article 20 of	30/05/2013	01/07/2013	SmPC and PL	Upon review of safety data and literature on immune disorders in association with antitretrovirals for the

	Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding autoimmune disorders in relation to Immune Reactivation Syndrome, following a class labelling for antiretrovirals as requested by the CHMP. The Package Leaflet was updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				treatment of HIV, the CHMP considered that there is sufficient evidence to conclude that immune reconstitution syndrome (IRS) after antiretroviral therapy may be associated with autoimmune disease/disorders even if the number of case reports is limited. Therefore, the CHMP had requested the inclusion of information on immune disorders under immune reconstitution as a class labelling for all antiretrovirals for the treatment of HIV.
IB/0056	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	15/05/2013	01/07/2013	SmPC, Labelling and PL	
IB/0057	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	29/04/2013	n/a		
X/0046	Addition of a 800 mg new strength. Annex I_2.(c) Change or addition of a new strength/potency	18/10/2012	14/01/2013	SmPC, Labelling and PL	Please refer to the assessment report H-707-X-46

IB/0053	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	29/11/2012	n/a		
II/0052	Update of section 4.5 of the SmPC with information on the potential drug drug interaction between darunavir and raltegravir following a request from the CHMP. The SmPC and Labelling have been updated following the approval of the 100 mg/ml oral suspension. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	01/07/2013	SmPC and Labelling	Some clinical studies suggest that raltegravir may cause a modest decrease in darunavir (Prezista) plasma concentrations; the mechanism for this effect is unknown. However, the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically relevant. Prezista co administered with low dose ritonavir and raltegravir can be used without dose adjustments.
II/0049	Update of section 4.5 of the SmPC with information on the drug interaction with artemether/lumefantrine. Section 2 of the PL was proposed to be updated in accordance. In addition, minor revisions to section 4.5 of the SmPC (drug interaction with boceprevir, co-administration with telaprevir) have been introducted. The MAH also took the opportunity to update the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	24/10/2012	SmPC and PL	Study TMC125VIR1001 conducted in 16 healthy male volunteers, evaluated the interaction of darunavir/ritonavir 600/100 mg b.i.d. with the anti-malarial fixed combination artemether/lumefantrine at a dose of 80/480 mg. Based on the obtained results, it can be concluded that the combination of Prezista and artemether/lumefantrine can be used without dose adjustments. However, due to the increase in lumefantrine exposure, the combination should be used with caution. No clinical relevant safety signal was detected in this limited dataset. The CHMP concluded that the benefit-risk balance of darunavir remains unchanged.

X/0041/G	This was an application for a group of variations. Update the section 4.1 of the SmPC for the existing 75mg, 150mg, 300mg, 600mg film coated tablets with the new paediatric indication (3 to 6 years weighing 15 to < 20 kg, HIV positive, treatment experienced patients) and introduce consequential changes to sections 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC for the existing 75mg, 150mg, 300mg, 400mg 600mg film coated tablets. The PL was updated accordingly. Changes to the product information were introduced in line with the QRD template. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency	19/07/2012	24/10/2012	SmPC, Annex II, Labelling and PL	Please refer to Assessment Report: H-707-X-41-G
IB/0050	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)	30/08/2012	14/01/2013	SmPC	
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
II/0047	Update of sections 4.4 and 4.8 of the SmPC with a new adverse drug reaction "acute generalised exanthematous pustulosis".	24/05/2012	27/06/2012	SmPC	Following a cumulative search of the safety database by the MAH, which retrieved three cases reporting acute generalised exanthematous pustulosis (AGEP) or rash pustular during the post-marketing experience, and taking

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				into account the known association between darunavir and severe skin reactions, the adverse drug reaction AGEP has been added in sections 4.4 and 4.8 of the SmPC.
IB/0048	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	12/04/2012	27/06/2012	SmPC and PL	Update of section 4.5 of the SmPC with new information on a drug drug interaction with boceprevir. It is not recommended to co-administer Prezista and boceprevir. The PL has been updated accordingly. Minor editorial changes to the French PL for the 300mg strenght were introduced.
II/0044/G	This was an application for a group of variations. Update of section 4.5 of the SmPC with new drug interaction with telaprevir and rilpivirine. The PL has been updated accordingly. In addition, the MAH took the opportunity to correct the resistance data for the 192 weeks results of Artemis in section 5.1 of the SmPC and to align the 400mg PL to the other strengths. In addition, the MAH took the opportunity to update the list of local representatives in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC and PL	The drug-drug interactions between darunavir and telaprevir and between darunavir and rilpivirine were assessed in two pharmacokinetic interaction studies already evaluated by the CHMP and reflected in the Product Information of Incivo (telaprevir) and Edurant (rilpivirine). The CHMP agreed to reflect the results of these studies of section 4.5 of Prezista. The PL was updated accordingly.
IA/0045	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing	16/12/2011	n/a		

	takes place				
II/0039	Update of Section 5.1 of the SmPC for the 400mg strength based on the 192-weeks efficacy and safety data from trial TMC114-C211 to further support the use of DRV/rtv 800/100 mg q.d. in ART-naïve adult patients in combination with other ARVs. In addition, for all the strengths (75mg, 150mg, 300mg, 400mg and 600mg), update of the Section 4.8 of the SmPC to reflect the data from this trial and update of the section 4 of the PL to align it with the existing Section 4.8 of the SmPC. The list of local representative in Austria has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC and PL	The week-192 analysis of trial TMC114-C211 demonstrate sustained virologic response and immunologic benefit of DRV/rtv 800/100 mg q.d. in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy (ART) naïve adults. The results confirm non-inferiority of the Prezista treatment regimen to Kaletra treatment regimen with regard to virologic response (confirmed plasma VL < 50 copies/mL) which was demonstrated at week 48 and confirmed by the week 96 analysis. No new safety signals were identified and the safety profile was in general comparable to that of week 48 and week 96. Section 4.8 was updated to reflect the median treatment duration.
IG/0090/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/07/2011	n/a		
II/0038	Update of section 4.5 of the SmPC with information regarding a new drug drug interaction with rosuvastatin in fulfilment of the request from the CHMP following the assessment of PSUR. The PL is	14/04/2011	18/05/2011	SmPC and PL	In an investigator sponsored drug drug interaction study, the steady state Cmax and AUC of rosuvastatin increased 2.44- and 1.48-fold respectively due to co-administration with DRV/rtv. The steady state pharmacokinetics of

	updated accordingly. In addition, the details from the local representatives in Belgium, Bulgaria and Latvia have been updated C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				DRV/rtv were not significantly altered due to co-administration with rosuvastatin. The co-administration of rosuvastatin and DRV/rtv slightly lowered the lipid-lowering effect of rosuvastatin administration alone. Hence, section 4.5 of the SmPC was updated with the interaction data and a recommendation that, when coadministration of DRV/rtv with rosuvastatin is required, the lowest possible dose of rosuvastatin should be used and titrated to clinical effect while monitoring for safety.
IB/0040/G	This was an application for a group of variations. 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.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 currently approved batch size 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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/03/2011	n/a		

II/0032	Extension of indication to add the treatment of antiretroviral experienced patients with no DRV resistance associated mutations (RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count more than 100 cells x 106/l to Section 4.1 of the 400mg tablet SmPC. Consequential changes have been introduced to sections 4.2, 4.4, 4.5 and 5.1 of the SmPC. Sections 4.4 and 4.5 of the SmPC have been updated to include information on interaction with efavirenz. In fulfilment of FUM 59, editorial changes have been made in section 5.1 of the SmPC. The other strengths are already authorised in ART-experienced adults i.e. 600/100 mg twice daily regimen for all other ART-experienced adults, including patients with more than 1 DRV RAMs and patients with no data on genotype. However, sections 4.1, 4.2, 4.4, 4.5, 5.1 have been updated in line with the changes on 400mg tablets. Annex IIB has been updated with a new version of the RMP. The DDPS version number has been removed. The PL has been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/01/2011	28/02/2011	SmPC, Annex II and PL	Study TMC114-C229 [ODIN] is a Week 48 data from a randomised (1:1 ratio), open-label non-inferiority trial comparing darunavir/ ritonavir (DRV/rtv) 800/100 mg q.d versus DRV/rtv 600/100 mg b.i.d (both in combination with an individually selected OBR consisting of more than 2 NRTIs) in treatment-experienced HIV-1 infected patients with screening genotype resistance testing showing no DRV RAMs. Based on the review of the clinical efficacy and safety of this study, the CHMP considers that the benefit-risk balance for DRV is positive for a restricted indication for the treatment of HIV 1 infection in ART-experienced adults with no drv resistance associated mutations (DRV RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count more than 100 cells x 106/l. In deciding to initiate treatment with DRV in such ART-experienced adults, genotypic testing should guide the use of DRV. The long-term data on the efficacy of the DRV/rtv q.d regimen in this population is not available. This is reflected in section 4.4 of the SmPC. In addition, sections 4.4 and 4.5 of the SmPC have been updated to inform the prescriber of the risks of suboptimal drv plasma trough concentrations and recommend the use of drv / rtv 600/100 mg b.i.d, instead of drv / rtv 800mg q.d, when drv is used in combination with efavirenz.
II/0037	Following the availability of updated pharmacokinetic information in the product information of medicines which could be co-administered with darunavir, sections 4.3 and 4.5 of the SmPC have been updated	21/10/2010	29/11/2010	SmPC and PL	Following the availability of updated pharmacokinetic information in the product information of medicines which could be co-administered with darunavir and low dose ritonavir:

	with a new contraindication with sildenafil used in PAH, sections 4.4 and 4.5 of the SmPC were updated with a new warning regarding the concomittant use of colchicine and section 4.5 of the SmPC with new recommendation regarding tadalafil when used in PAH, bosentan and salmeterol. The PL has been updated accordingly. In addition, a minor inconsistency was corrected in Section 5.2 of the SmPC for the 400mg strenght and the address of the local reprentatives in Belgium and Luxembourg were updated in the PL. Translation mistakes affecting all the languages are being corrected with the present application. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				" Sections 4.3 and 4.5 of the SmPC have been updated with a new contraindication with sildenafil used in pulmonary arterial hypertension (PAH), " Sections 4.4 and 4.5 of the SmPC were updated with a new warning regarding the concomitant use of colchicine, " Section 4.5 of the SmPC with a new recommendation regarding the concomitant use of tadalafil when used in PAH (co-administration not recommended with darunavir and low dose ritonavir), " Section 4.5 of the SmPC with a new recommendation regarding the concomitant use of bosentan (the patient's tolerability of bosentan should be monitored when administrated with darunavir and low dose ritonavir), " Section 4.5 of the SmPC with a new recommendation regarding the concomitant use of salmeterol (increased risk of cardiovascular adverse event when salmetrol is used with darunavir and low dose ritonavir).
IG/0023/G	This was an application for a group of variations. C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the	21/09/2010	n/a	Annex II	

	DD				
IB/0036	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	23/07/2010	n/a	SmPC, Annex II and PL	Addition of warning to section 4.4 of the SPC and a paragraph to section 4.8 of the SPC regarding the potential for a higher than expected rate of rash when raltegravir is co-administered with darunavir. PL updated accordingly.
IB/0035/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	23/07/2010	n/a	SmPC and PL	Further to PI of ritonavir update with the addition of alfuzosin as contraindication in the SmPC; MAH is applying to amend sections 4.3 and 4.5 of the SmPC and section 2 of the PL to add alfuzosin as a contraindication in the Prezista PI also. Addition of dosage recommendation to section 4.5
IA/0034	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	14/07/2010	n/a	Annex II	
II/0029	Update of sections 4.4 and 4.8 of the SmPC to align them according to the revised Guideline on SmPC dated September 2009 and to implement changes made to the Company Core Data Sheet (CCDS) (dated October 2009) based on a review of the MAH's safety database following the CHMP's assessment of PSUR 4. Further updates of sections 3, 4.2, 4.5, 4.7, 5.1 and 5.2 of the SmPC in order to align according to the Guideline on SmPC as well. The PL was revised accordingly.	22/04/2010	02/06/2010	SmPC and PL	Major changes affected sections 4.4 and 4.8 of the SmPC based on the requirements to both implement the revised guideline on SmPC and to update the SmPC content in line with the latest version of the CCDS. Consequently to the review of the company safety database and the post-marketing data, new ADRs were added to both section 4.4 (severe skin reactions and hepatotoxicity) and section 4.8 (drug hypersensitivity, osteonecrosis, toxic epidermal necrolysis (TEN) and angioedema). Section 4.8 was also revised to include the 3 subsections, as per guideline, and

	Update of Summary of Product Characteristics and Package Leaflet				to update the ADR table with the new frequency estimates.
IB/0033/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 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	31/03/2010	n/a		
II/0030	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	18/02/2010	15/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 005) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted

					DDPS contained all required elements.
II/0027	Update of sections 4.8 and 5.1 of the SPC based on the 96-week data from study TMC114-C211 (ARTEMIS), in fulfilment of the CHMP's request regarding follow-up measure 024.1. In addition, the MAH took this opportunity to update the SPC and PL of the 400mg strength to introduce cross-references to the recently approved paediatric strengths (75 & 150mg). Finally, a minor typographical error in the PL was corrected. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	23/10/2009	SmPC and PL	The Week-96 efficacy and safety results of the ARTEMIS study were in line with Week-48 primary analysis results in the treatment of ART treatment naïve HIV-1 infected adult patients. The results demonstrated non-inferiority of the darunavir/ritonavir treatment regimen to lopinavir/ritonavir treatment regimen with regard to virologic response (confirmed plasma VL < 50 copies/ml). Also, the Week-96 safety data were consistent with those in the Week-48 analysis. No substantial changes in the incidence of adverse events were observed compared to the Week-48 data. Nevertheless, section 4.8 was updated to add 9 adverse reactions that had only now clearly shown their relatedness with darunavir/ritonavir.
II/0026	Update of section 5.1 of the SPC based on the 96 week final study report from study TMC114-C214, in fulfilment of the CHMP's request regarding follow-up measure (FUM) 003.1. This variation also addresses FUM 040, to align the content of section 5.1 in line with Annex B to the revised CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection. Update of Summary of Product Characteristics	24/09/2009	23/10/2009	SmPC	The Week-96 efficacy and safety results of the TITAN study were in line with Week-48 primary analysis results in the treatment of ART treatment experienced HIV-1 infected adult patients. The results demonstrated non-inferiority of the darunavir/ritonavir treatment regimen to lopinavir/ritonavir treatment regimen with regard to virologic response (confirmed plasma VL < 400 copies/ml). Also, the Week-96 safety data were consistent with those in the Week-48 analysis. No substantial changes in the incidence of adverse events were observed compared to the Week-48 data.
II/0024	Update of section 4.5 of the SPC and section 2 of the PL based on a drug-drug interaction study exploring the interaction of darunavir/ritonavir with buprenorphine/naloxone. Furthermore, the MAH aligned section 4.5 of the SPC in line with Annex A to	24/09/2009	23/10/2009	SmPC, Labelling and PL	In this study a total of 17 patients who were on stable buprenorphine/naloxone maintenance therapy for at least 2 weeks received darunavir/ritonavir at 600/100 mg twice a day for 7 days added to their buprenorphine/naloxone therapy. The results of this study demonstrated that

	the revised CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02 Rev.2). In addition, contact details of local representatives were updated in the PL. Finally, CYP3A4 has been replaced by CYP3A in order to be consistent throughout the product information. Update of Summary of Product Characteristics, Labelling and Package Leaflet				buprenorphine and naloxone exposure was comparable for buprenorphine/naloxone administered with or without darunavir/ritonavir. In contrast, norbuprenorphine (a buprenorphine metabolite) exposure was increased when buprenorphine/naloxone was coadministered with darunavir/ritonavir, compared to buprenorphine/naloxone administered alone. Mean darunavir and ritonavir exposure in the presence of buprenorphine/naloxone were comparable with historical data. As no opioid toxicity specific adverse reactions in relation to the increase in norbuprenorphine were detected, the clinical relevance of this finding has not been established. Dose adjustment for buprenorphine may not be necessary when co-administered with darunavir/ritonavir but a careful clinical monitoring for signs of opiate toxicity is recommended.
II/0028	To introduce a minor change in the manufacturing process and test procedure of the active substance and to extend the drug substance retest period Quality changes	24/09/2009	29/09/2009		
X/0021	Annex I_2.(c) Change or addition of a new strength/potency	23/04/2009	23/06/2009	SmPC, Labelling and PL	Please refer to the scientific conclusions: Prezista-H-707-X-20&21-AR.
X/0020	Annex I_2.(c) Change or addition of a new strength/potency	23/04/2009	23/06/2009	SmPC, Labelling and PL	Please refer to the scientific conclusions: Prezista-H-707-X-20&21-AR.
II/0025	Extension of indication for Prezista 300 mg and 600 mg film-coated tablet to include the treatment of HIV-1 infection in ARV treatment experienced	23/04/2009	23/06/2009	SmPC and PL	Based on the review of the efficacy and safety of darunavir/ritonavir in children and adolescents above the age of 6 years (clinical trial TMC114-C212), the CHMP

	adolescents and children of 6 years and above and with a body weight of more than 20 kg. Extension of Indication				agreed to extend the indication of Prezista to include this antiretroviral therapy experience patient group. For details of this assessment, please refer to the scientific conclusions: Prezista-H-707-X-20&21-AR. The availability of the DRV 300 mg and 600 mg tablet strengths, next to the newly introduced 75 mg and 150 mg tablet strengths, represents a therapeutic advance for HIV-1 infected treatment experienced paediatric adolescents and children of 6 years and above and with a body weight of more than 20 kg, as it enhances patient comfort and convenience (flexible dosing and reduced pill burden) leading to a higher chance of treatment adherence. Therefore, the CHMP agreed to extend the indication to include the treatment of these paediatric patients and agreed to the changes introduced in the Prezista Product Information.
X/0019	The MAH applied for an additional strength of 600 mg film-coated tablets. Annex I_2.(c) Change or addition of a new strength/potency	20/11/2008	29/01/2009	SmPC, Annex II, Labelling and PL	The MAH applied for a Marketing Authorisation for a new strength: the 600 mg film-coated tablet to address unmet clinical needs.
X/0016	The MAH applied for an additional strength of 400 mg film-coated tablets. This new strength is indicated for the treatment of antiretroviral therapy naïve HIV-infected adults. Annex I_2.(c) Change or addition of a new strength/potency	20/11/2008	29/01/2009	SmPC, Annex II, Labelling and PL	Please refer to the scientific conclusions: Prezista-H-707-X-16-AR

II/0015	Update of section 4.4 and 4.8 of the SPC based on safety data from Phase IIb and Phase III trials. Section 4 of the PL is updated in accordance. The MAH also took this opportunity to propose a minor editorial change to section 4.5. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	22/12/2008	SmPC and PL	The CHMP disagreed with the MAH's conclusion that the merging of the data for experienced and naïve patients was medically and scientifically viable and found the combined analysis therefore not acceptable. The MAH was therefore requested to retain the original information of the darunavir/ritonavir safety profile. Nevertheless, the CHMP agreed to introduce a paragraph highlighting the safety results in the new patient population of treatment naïve patients. In addition, the CHMP requested that section 4.8 be brought fully in line with the Guideline on SPC.
II/0010	Update of section 4.5 of the SPC based on a pharmacokinetic interaction study between rifabutin and darunavir, co-administered with ritonavir. The study is submitted at the request of the CHMP in the frame of a follow up measure. Update of Summary of Product Characteristics	20/11/2008	22/12/2008	SmPC	In this study, exposure of darunavir/ritonavir was increased due to concomitant treatment with rifabutin. Based upon data from previous submitted studies, a dose adjustment for darunavir/ritonavir was not recommended. For rifabutin a pronounced effect was observed, with an about 10-fold increase in the active 25-O-desacetylrifabutin metabolite. The results obtained in this trial for the differential effect of co-administration of darunavir/ritonavir on rifabutin and 25-O-desacetylrifabutin exposure are consistent with that observed for other ritonavir boosted PIs given in combination with rifabutin 150 mg q.o.d.. Consequently, a dose reduction of rifabutin was recommended, and a warning added that increased monitoring for rifabutin related adverse events is warranted.
R/0022	Renewal of the marketing authorisation.	23/10/2008	16/12/2008	SmPC, Annex II, Labelling and PL	
II/0014	Extension of the therapeutic indication to include moderately antiretroviral treatment experienced patients. In addition, the MAH took this opportunity	23/10/2008	25/11/2008	SmPC and PL	Please refer to the scientific conclusions: Prezista-H-707-II-14-AR

	to update contact details of local representatives in the PL. Extension of Indication				
II/0023	Update of section 4.3 and section 4.5 of the SPC to implement the class labelling text agreed by the CHMP in May 2008 on the combination of rifampicin with darunavir given with concomitant low-dose ritonavir. Update of Summary of Product Characteristics	25/09/2008	24/10/2008	SmPC	In 2005 an interaction study on saquinavir boosted with ritonavir together with rifampicin in healthy volunteers had to be prematurely discontinued due to an increased risk of hepatotoxicity associated with this co-administration. The mechanism for this interaction is not fully elucidated. It has been hypothesised that the predominant effect between the inducer effect of rifampicin and the inhibitor effect of the boosted protease inhibitors might depend on the boosted protease inhibitor involved. Lacking the results of specific interaction studies, the CHMP concluded as a conservative measure to reinforce the contraindication with rifampicin in section 4.4 and improve the guidance provided to physicians regarding the interaction of boosted protease inhibitors with rifampicin in section 4.5.
II/0018	Update of section 4.5 of the SPC based on two studies elucidating the interaction of darunavir with cytochromes CYP2C9, CYP2C19, CYP2D6 and CYP2C8, as requested by the CHMP in February 2008 following the assessment of follow-up measures 020 and 022.1. Update of Summary of Product Characteristics	24/07/2008	29/08/2008	SmPC	A clinical study utilising a mixture of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir; this was attributed to the presence of low-dose ritonavir. Co-administration of darunavir/ritonavir and medicinal products which are primarily metabolised by CYP2D6 may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by

					CYP2C9 and CYP2C19 may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect. Although the effect on CYP2C8 has only been studied in vitro, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.
II/0012	Update of section 5.1 of the SPC to provide information on the resistance profile of darunavir. This Type II variation is resulting from the FUM 023 to provide ongoing updated analyses on the emergence of resistant strains and data on cross resistance between darunavir and other Protease Inhibitors. Update of Summary of Product Characteristics	26/06/2008	28/07/2008	SmPC	The pooled analysis of the results from the pivotal trials together with the results from the DUET studies, excluding the results of the arms receiving combination therapy with etravirine provided confirmatory information on the resistance profile of darunavir in highly antiretroviral therapy (ART) patients. These analysis confirmed that baseline darunavir fold change in EC50 value and presence of at least 3 darunavir resistance-associated mutations at baseline impact on the virological response in the studied highly ART experienced HIV-1 population. In addition, virologic failures were associated with the development of additional protease mutations during treatment with darunavir in combination with Optimized Background Therapy. The finding that 70.5% of the isolates from rebounders that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment with DRV/RTV is of clinical importance in considering tipranavir for salvaging subjects based on resistance testing of patients failing darunavir.
II/0017	Update the section 4.5 of the SPC regarding the interaction of darunavir/ritonavir with	30/05/2008	04/07/2008	SmPC and PL	The results of the interaction study TMC114-C172 indicated that darunavir pharmacokinetics are not significantly

	carbamazepine. Section 2 of the PL is updated accordingly. In addition, the Marketing Authorisation Holder took this opportunity to update section 6 of the PL with new contact details for the local representative in Romania. Update of Summary of Product Characteristics and Package Leaflet				affected when darunavir/ritonavir is combined with carbamazepine. Carbamazepine decreased the plasma exposure of ritonavir significant by about 50%. However, the darunavir levels were not affected indicating that the boosting effect of ritonavir was still maintained. Darunavir and ritonavir inhibition of CYP3A4 resulted in increased levels of carbamazepine which may lead to an increase in carbamazepine-related adverse events. Therefore, it was recommended that patients should be monitored, that carbamazepine concentrations should be monitored and that its dose should be titrated for adequate response. In addition, based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/ritonavir.
II/0011	Update of section 5.3 of the SPC based on darunavir carcinogenicity studies. The studies are submitted in fulfilment of a follow up measure. Update of the PL with new contact details for the local representatives in Estonia, Ireland, Latvia, Lithuania, Malta and United Kingdom. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	The results of the two 24-month carcinogenicity studies in rats and in mice and the results of the study relating to the effects on pituitary-thyroid axis for 1 month oral administration in rats suggest that, in the rat, the occurrence of liver and thyroid tumours is likely related to enzyme induction. They also reveal that the liver tumours in mice might be caused by enzyme induction. Therefore, it was concluded that the liver tumours in mice and the liver and thyroid tumours in rats are likely not relevant for humans. The results of these studies were reflected in section 5.3 of the SPC.
II/0013	Quality changes	30/05/2008	05/06/2008		This variation application was submitted in order to optimise the manufacturing process of intermediates and of the drug substance. As a result of this optimisation, some consequential changes have been submitted.

					Also an alternative secondary packaging material is proposed for the container of the drug substance. None of the changes affect the benefit-risk balance of this product.
R/0008	Renewal of the marketing authorisation.	15/11/2007	10/01/2008	SmPC, Annex II, Labelling and PL	The CHMP reviewed the available information on the status of the fulfilment of the Specific Obligations by the MAH. The Committee confirmed that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated, and that its benefit risk balance remains positive. The Committee recommended that the Marketing Authorisation remains 'conditional' until the remaining specific obligations are fulfilled.
II/0009	Update of section 5.3 of the SPC based on two toxicity studies in juvenile rats as requested by the CHMP in June 2007. In addition, the MAH took this opportunity to clarify a terminology in both the SPC and the Package Leaflet. Contact details for the local representatives in Malta, Germany, Poland and Latvia in the PL are also updated. Update of Summary of Product Characteristics and Package Leaflet	15/11/2007	18/12/2007	SmPC and PL	The results of the two toxicity studies suggest that the exposure in rats aged 5-11 days is higher than in adult rats. After 23 days of age, it is comparable to adult rats. The high exposure at young age and the subsequent decrease in exposure from postnatal day 8 onwards is probably related to the maturation of the liver metabolising enzymes and the blood brain barrier. Data show further that it cannot be excluded that toxicity was higher in animals aged 5-11 days than in adult animals. In animals aged 23-50 days, toxicity was not higher than in adult animals. The presented preclinical results suggest that comparable doses may cause a higher exposure in very young children compared to adults, which may result in a higher risk of toxicity.
II/0007	Update of sections 4.2, 4.4 and 5.2 of the SPC based on the final results of a study assessing the pharmacokinetics and the safety of multiple doses of	15/11/2007	18/12/2007	SmPC	The final study report describing the pharmacokinetics and safety of darunavir with low-dose ritonavir in patients with mild and moderate hepatic impairment was provided by the

	darunavir/ritonavir in patients with impaired hepatic function. Update of Summary of Product Characteristics				MAH. These pharmacokinetic data confirmed the preliminary information already reflected in the SPC. However, the concentration-dependent protein binding (AAG) of darunavir was also confirmed. The increase in free fraction of AAG is not considered as an issue for the efficacy, however safety may be affected. Therefore, darunavir should be used with caution in patients with impaired hepatic function. The free fraction of darunavir may be increased in patients with mild to moderate hepatic dysfunction due to lower AAG.
II/0006	Update of sections 4.3 and 4.5 of the SPC based on the results from a study on the pharmacokinetic interaction between darunavir, lopinavir and ritonavir in HIV-1 infected patients. Section 2 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	27/08/2007	SmPC and PL	Results from a study designed to evaluate the pharmacokinetic interaction between darunavir, lopinavir and ritonavir in HIV-1 infected patients showed that lopinavir causes large decreases in darunavir concentrations, which may significantly affect the therapeutic effect of darunavir. This effect was not compensated by the administration of increased doses of darunavir. Therefore, the co-administration of darunavir with the combination lopinavir/ritonavir is contra-indicated.
II/0005	Update of section 4.5 of the SPC the based on a study in patients on a stable methadone maintenance therapy investigating the pharmacokinetic interaction between methadone and darunavir/ritonavir at steady-state. Update of Summary of Product Characteristics	19/07/2007	27/08/2007	SmPC	The interaction between darunavir/ritonavir and methadone was studied in a pharmacokinetic study. Sixteen patients receiving their once daily methadone maintenance therapy were included in this study. Darunavir/ritonavir was co-administered for 7 days. Based upon the results of this study a dose adjustment is not considered necessary when starting co-medication of darunavir/ritonavir and methadone. However in this study the interaction phase of 7 days was relatively short and the number of patients was limited. Therefore, a further decrease in methadone plasma levels at a later stage cannot be excluded and clinical

					monitoring upon continued combination is recommended.
II/0004	Update of section 4.5 of the SPC based on a study in healthy volunteers investigating the pharmacokinetic interaction between didanosine and darunavir/ritonavir at steady-state. Update of Summary of Product Characteristics	19/07/2007	27/08/2007	SmPC	The interaction between darunavir/ritonavir and didanosine was studied in a pharmacokinetic study. Seventeen patients completed this study. Patients received darunavir/ritonavir for 7 days, didanosine for 7 days, and darunavir/ritonavir co-administered with didanosine for 7 days. Treatments were separated by a washout period of 7 days. No clinical significant differences were observed in the pharmacokinetics of darunavir and ritonavir after co-administration with didanosine.
II/0002	Update of sections 4.3 and 4.5 of SPC and section 2 of the PL as regards the interaction with oral and parenteral midazolam, following CHMP request in March 2007. Contact details of the local representative in Bulgaria were updated in section 6 of the PL Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Based on available data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally than when it is injected. Therefore, the coadministration of Prezista with orally administered midazolam is contraindicated, whereas caution should be used when Prezista is co-administrated with injection of midazolam. If Prezista is co-administered with injectable midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. Sections 4.3 and 4.5 of the SPC and section 2 of the PL are updated with this information.
II/0003	Quality changes	19/07/2007	23/07/2007		