Reyataz

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
II/0137	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023	25/08/2023	SmPC and PL	The Product Information has been updated to include information on the contraindication with apalutamide and co-administration of Reyataz and antiplatelet therapies classified as P2Y12 platelet inhibitors (ticagrelor, clopidogrel and prasugrel), dexamethasone or other corticosteroids, antineoplastics (encorafenib or ivosidenib),

[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).

					gonadotropin-releasing hormone (GnRH) receptor antagonist (elagolix), kinase inhibitor (fostamatinib) and antineoplastic (apalutamide). For more information, please refer to the Summary of Product Characteristics and Package Leaflet.
WS/2498/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. 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.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	13/07/2023	n/a		
IB/0136	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/10/2022	23/01/2023	SmPC and PL	
IB/0135/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.2.a - Change to importer, batch release	01/08/2022	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.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				
IAIN/0134/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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	16/02/2022	23/01/2023	Annex II and PL	
PSUSA/258/202106	Periodic Safety Update EU Single assessment - atazanavir	10/02/2022	n/a		PRAC Recommendation - maintenance
N/0133	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/10/2021	23/01/2023	PL	
IB/0131	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/11/2020	n/a		
II/0129/G	This was an application for a group of variations.	23/07/2020	28/08/2020	SmPC, Annex	SmPC new text

	Grouped application: - C.I.4 (Type IB) - Update of sections 4.3 and 4.5 of the SmPC to add a new contraindication and a new drug-drug interaction related to co-administration with lomitapide, based on recommendations already approved for lomitapide; the Package Leaflet is updated accordingly. - C.I.4 (Type II) - Update of section 4.5 of the SmPC to add new drug-drug interactions related to co-administration with the direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban and rivaroxaban, to align with wording approved for DOACs; the Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the PI in line with the Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev.1) regarding sucrose content, remove boceprevir from Section 4.5 of the SmPC and Section 2 of the PL, bring the PI in line with the latest QRD template version 10.1 and 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			II and PL	Lomitapide is highly dependent on CYP3A4 for metabolism and co-administration with REYATAZ with ritonavir may result in increased concentrations. Co-administration of lomitapide and REYATAZ with ritonavir is contraindicated due to a potential risk of markedly increased transaminase levels and hepatotoxicity. Potential for increased apixaban and rivaroxaban concentrations which can result in a higher risk of bleeding. The mechanism of interaction is inhibition of CYP3A4 / and P-gp by REYATAZ/ritonavir. Ritonavir is a strong inhibitor of both CYP3A4 and P-gp. REYATAZ is an inhibitor of CYP3A4. The potential inhibition of P-gp by REYATAZ is unknown and cannot be excluded. Co-administration of apixaban or rivaroxaban and REYATAZ with ritonavir is not recommended Potential for increased dabigatran concentrations which can result in a higher risk of bleeding. The mechanism of interaction is P-gp inhibition. Ritonavir is a strong P-gp inhibitor. Potential P-gp inhibition by REYATAZ is unknown and cannot be excluded. Co-administration of dabigatran and REYATAZ with ritonavir is not recommended. Potential for increased edoxaban concentrations which can result in a higher risk of bleeding. The mechanism of interaction is P-gp inhibition by REYATAZ/ritonavir. Ritonavir is a strong P-gp inhibitor. Potential P-gp inhibition by REYATAZ is unknown and cannot be excluded. Exercise caution when edoxaban is used with REYATAZ. For more information, please refer to the Summary of Product Characteristics.

IAIN/0130/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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	15/05/2020	28/08/2020	Annex II and PL	
IG/1193	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/01/2020	n/a		
IAIN/0127	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	12/12/2019	n/a		
IA/0126	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	23/10/2019	n/a		
IB/0125/G	This was an application for a group of variations.	01/08/2019	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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				
IA/0124	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	14/05/2019	n/a		
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	13/03/2019	SmPC, Labelling and PL	
PSUSA/258/201806	Periodic Safety Update EU Single assessment - atazanavir	17/01/2019	n/a		PRAC Recommendation - maintenance
IA/0122/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	04/01/2019	n/a		

	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
II/0117	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	29/11/2018	n/a		

	of studies to the competent authority				
IAIN/0121	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2018	31/01/2019	SmPC	
IA/0119/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	03/10/2018	n/a		
IB/0118	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/09/2018	31/01/2019	SmPC and PL	
WS/1292	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 and 4.5 of the SmPC in order to add a contraindication with lurasidone to reflect this interaction based on literature data. The Package Leaflet is updated accordingly. The RMP of Reyataz/Evotaz versions 14.1 and 6.1 respectively have been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to	22/02/2018	31/01/2019	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IG/0889	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	13/02/2018	n/a		
WS/1193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update sections 4.3 and 4.5 of the SmPC to include information on the contraindicated co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination (used to treat chronic hepatitis C infection) reflecting the results of interaction studies. The Package Leaflets are updated accordingly. The RMP versions 13.2 and 5.0, for Reyataz and Evotaz respectively have been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes and typographical corrections in the REYATAZ and EVOTAZ Product Information. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk	26/10/2017	11/12/2017	SmPC and PL	

	Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0115	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	30/11/2017	n/a		
II/0111	Update of sections 4.4 and 4.8 of the SmPC to add a warning on chronic kidney disease observed in HIV infected patients during treatment with atazanavir (with or without ritonavir). This update is based on a review of the MAH safety database, a cohort study of patients with laboratory values from a large US administrative claims database and a review of published scientific literature. The Package Leaflet is updated accordingly. The RMP version 12.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2017	11/12/2017	SmPC and PL	Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. This has been shown in a large prospective observational study with an association between an increased incidence of chronic kidney disease and cumulative exposure to atazanavir/ritonavir-containing regimen in HIV-infected patients with an initially normal eGFR. This association was observed independently of exposure to tenofovir disoproxil. Regular monitoring of the renal function of patients should be maintained throughout the treatment duration. The product information and the Risk management plan are updated with the above information.
IG/0795	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	04/05/2017	n/a		
IB/0108/G	This was an application for a group of variations.	30/01/2017	n/a		

	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.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				
IA/0109	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/01/2017	n/a		
IB/0106/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	15/12/2016	n/a		
II/0105/G	This was an application for a group of variations. Scope C.I.4 Update of section 4.6 of the SmPC in order to update the safety information on lactation to indicate that atazanavir has been detected in human milk. The Package Leaflet and the RMP (version 11.0) are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.	15/12/2016	11/12/2017	SmPC and PL	

	Scope C.I.11.b This type II variation aims to update the RMP (version 11.0) in order to add "IRIS" and "angioedema" to Important Identified Risks and to update the epidemiology/exposure sections. The MAH also took the opportunity to make some reformatting changes to align the RMP with the current approved EMA template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				
IB/0107	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/11/2016	n/a		
IA/0104	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	02/09/2016	n/a		
X/0094/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new	28/04/2016	21/06/2016	SmPC, Annex II and PL	For further information please refer to: Reyataz-H-C-494-X-94-G-en.

	strength/potency 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0103	B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	20/06/2016	n/a		
PSUSA/258/201506	Periodic Safety Update EU Single assessment - atazanavir	11/02/2016	n/a		PRAC Recommendation - maintenance
WS/0889	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	21/06/2016	SmPC and PL	
IG/0636	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/12/2015	n/a		
IB/0099	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	27/11/2015	21/06/2016	SmPC, Labelling and PL	

	the range of the currently approved pack sizes				
II/0096	Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 5.1 and 5.2 of the SmPC in order to provide important information and guidance to prescribers when they consider using unboosted atazanavir (ATV) in line with international guidelines (i.e. when they consider withdrawing ritonavir from the boosted ATV regimen) based on study INDUMA/AI424-136. In addition, the MAH took the opportunity to make a minor change in section 4.7 of the SmPC for increased clarity, and minor editorial changes to the SmPC and PL. The RMP version 9.1 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC and PL	The recommended standard treatment is REYATAZ boosted with ritonavir, ensuring optimal pharmacokinetic parameters and level of virologic suppression. The withdrawal of ritonavir from the boosted regimen of REYATAZ is not recommended, but may be considered in adults patients at the dose of 400 mg once daily with food only under the following combined restrictive conditions: absence of prior virologic failure, undetectable viral load during the last 6 months under current regimen and viral strains not harbouring HIV resistance associated mutations (RAMs) to current regimen. REYATAZ is contraindicated in patients with severe hepatic insufficiency. REYATAZ with ritonavir is contraindicated in patients with moderate hepatic insufficiency. In case of withdrawal of ritonavir from the recommended atazanavir boosted regimen the same recommendations for drug drug interactions would apply except that co-administration is not recommended with tenofovir, boceprevir, carbamazepine, phenytoin, phenobarbital, proton pump inhibitors, and buprenorphine and that co-administration with famotidine is not recommended but if required, atazanavir without ritonavir should be administered either 2 hours after famotidine or 12 hours before. No single dose of famotidine should exceed 20 mg, and the total daily dose of famotidine should not exceed 40 mg. Moreover, there is a need to consider that co-administration of voriconazole and REYATAZ without ritonavir may affect atazanavir concentrations; co-administration of fluticasone and REYATAZ without ritonavir

					may increase fluticasone concentrations relative to fluticasone given alone; no dose adjustment of lamotrigine is required. Finally, if an oral contraceptive is administered with REYATAZ without ritonavir, it is recommended that the oral contraceptive contain no more than 30 µg of ethinyloestradiol. This is because unboosted atazanavir increases the exposure to ethinyloestradiol and norethindrone given in combination. The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance. REYATAZ given without ritonavir should not be used in pregnant patients given that it could result of suboptimal exposure of particular concern for the mother infection and vertical transmission. For efficacy and pharmacokinetic (including patients with hepatic impairment) information from study INDUMA/AI424-136 employing unboosted atazanavir please refer to the SmPC.
IG/0602	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)	11/09/2015	n/a		
IB/0095	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	24/06/2015	n/a		
IB/0093	B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a	26/11/2014	n/a		

	specification parameter as a result of a safety or quality issue				
II/0090	Update of sections 4.4 to include a warning on cholelithiasis and add information on nephrolithiasis and included interstitial nephritis as an adverse reaction in 4.8 of the SmPC. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2014	19/02/2015	SmPC, Annex II and PL	Based on a safety review of the MAH Corporate Adverse Event Reporting and Evaluation System (CARES) database and the literature, the MAH submitted this variation application to add cholelithiasis, as well as the following information on nephrolithiasis to the section 4.4: "Some patients required hospitalization for additional management and some had complications. In some cases, nephrolithiasis has been associated with acute renal failure or renal insufficiency." Furthermore, based on the safety review, interstitial nephritis has been added as an adverse reaction in the post-marketing experience of section 4.8 of the Reyataz SmPC.
WS/0539	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 4.4 of the SmPC to revise the wording regarding the risk of sexual transmission of HIV infection following CHMP request adopted in December 2013. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the details of the local representatives for Croatia and to incorporate the Croatian language annexes for Zerit. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/03/2014	19/02/2015	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.

IB/0091	B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	04/12/2013	n/a		
II/0089	Update of SmPC section 4.5 with information about possible interactions with antiepileptic medicines carbamazepine, phenytoin, phenobarbital and lamotrigine. The Package Leaflet has been amended accordingly. In addition, drug-drug interaction data with quetiapine and the consequent contradiction for use of this combination was included in the SmPC sections 4.3 and 4.5, as requested by the CHMP. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to align the PI with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	25/11/2013	SmPC and PL	Atazanavir (ATV) has a complex interaction profile. On one hand, it is a substrate of CYP3A4 and then, drugs that induce CYP3A4 may decrease plasma concentrations of ATV and potentially reduce its therapeutic effect. On the other hand, ATV is an inhibitor of cytochrome P450 (CYP) 3A4 and UGT1A1, and a weaker inhibitor of CYP2C8. Hence, coadministration of ATV and drugs primarily metabolized by CYP3A4 or UGT1A1 may result in increased plasma concentrations of the other drug that could result in increased or prolonged therapeutic and/or adverse effects. The update of the product information is to include potential and observed drug interactions between ATV boosted with low dose ritonavir (rtv) and the antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and lamotrigine. No clinical DDI studies were submitted. The proposed SmPC changes are based on the pharmacokinetic features of each compound towards CYPs and UGTs enzymes. Drug-drug interaction with quetiapine resulting in deep come was identified as a signal and as a consequence the CHMP endorsed the PRAC recommendation to add this information in section 4.5 and include the contra-indication for concomitant use with quetiapine.

WS/0388	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 4.4 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 PL was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL. 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	30/05/2013	21/06/2013	SmPC and PL	Upon review of safety data and literature on immune disorders in association with antitretrovirals for the 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.
II/0087	Update of section 4.8 of the Summary of Product Characteristics in order to update the safety information related to angioedema. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	25/11/2013	SmPC and PL	In December 2012, the Committee for Medicinal Products for Human Use endorsed the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation to perform a cumulative review of angioedema (angioedema - narrow standard MedDRA queries [SMQs]) and anaphylactic reaction (anaphylactic reaction - narrow SMQs) associated with ATV. As a consequence, the MAH performed 2 separate analyses, one focusing on angioedema and a second on anaphylactic reaction. The cumulative review on angioedema concluded that there is causal relationship between the administration of atazanavir and the occurrence of angioedema, which

					warranted an update of the Reyataz Product Information. Since the preferred terms rash, pruritus and urticaria were listed in the section 4.8 of the SmPC, the addition of angioedema as an adverse drug reaction was considered relevant. The cumulative analysis of anaphylactic reactions reported with atazanavir identified a total of 7 cases which were poorly documented to identify a causal relationship with ATV. Therefore, the addition of anaphylactic reaction was not considered necessary. The MAH will continue to closely monitor anaphylactic reactions.
II/0084	Update of sections 4.4 and 4.5 of the SmPC in order to revise the warning and update drug-drug interaction study results for the co-administration of atazanavir/ritonavir (ATV/RTV) with voriconazole (VOR). In addition, the Annex II was updated according to the latest QRD template and typographic errors were corrected in the Package Leaflet (PL). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	21/06/2013	SmPC, Annex II and PL	Study AI424383 was performed to assess the effect ATV/RTV on voriconazole pharmacokinetics and vice versa. Because CYP2C19 is subject to polymorphism the study enrolled patients with both status, extend metabolizers (n=24) and poor metabolizers (n=8). Study results with the interaction between atazanavir/ritonavir and the antifungal voriconazole are reflected on section 4.5 of the SmPC and the warning and precaution section 4.4 was amended with information on patients without a functional CYP2C19 allele.
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0085/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	14/11/2012	n/a		

	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 takes place				
II/0082	Update of sections 4.3, 4.4 and 4.5 of the SmPC with information on drug-drug interaction with statins. The PL has been updated accordingly. 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	23/08/2012	SmPC and PL	Following the availability of new drug-drug interaction and safety data, the co-administration of Reyataz with simvastatin or lovastatin was contraindicated due to an increased risk of myopathy including rhabdomyolysis (section 4.3 of the SmPC). Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors, including Reyataz, and this was reflected in section 4.5 of the SmPC. Concerning interactions with atorvastatin, the CHMP recommended not to co-administer it with atazanavir/ritonavir, because preferring a statin not metabolised by the CYP3A4 in HIV patients was considered a safer approach (section 4.5 of the SmPC). Additional guidance on the co-administration with Atorvastatin was added in section 4.5 in consideration of those patients already undergoing such treatment or for which such treatment is strictly necessary.
IA/0083/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test procedure is already authorised	13/07/2012	n/a		

II/0080	Update of sections 4.4 and 4.5 of the SmPC with dose adjustment when Reyataz is co-administered with both famotidine and tenofovir disoproxil fumarate. This type II variation is submitted in fulfilment of FU2 0073.1 (submission of Final CSR AI424398). In addition a statement concerning the co-administration of Reyataz with certain types of hormonal contraceptives (already discussed in section 4.5) was added in section 4.4. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	28/06/2012	SmPC, Annex II, Labelling and PL	Reyataz (atazanavir, ATV) exhibits pH-dependent solubility with decreased solubility at higher pH. Therefore, the absorption of ATV may be reduced if gastric pH is increased, e.g. when co-administered with an acid-reducing agent such as an H2-receptor antagonist. Results from the drug-drug interaction study AI424398 demonstrated that when the H2-receptor antagonist famotidine (FAM) is co-administered at doses up to 40 mg twice daily in HIV-infected patients taking ATV/ritonavir (RTV)/tenofovir disoproxil fumarate (TDF) and at least one other nucleoside reverse transcriptase inhibitor (NRTI), increasing the ATV dose to 400 mg will provide ATV exposures similar to or slightly higher than ATV exposures previously demonstrated to be efficacious. These data support a dosing regimen of ATV/RTV/TDF 400/100/300 mg once daily with at least one other NRTI when co-administration of H2-receptor antagonists is necessary.
IB/0081	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	28/06/2012	SmPC and PL	Update of section 4.5 of the SmPC with new information on a drug drug interaction with boceprevir. Co-administration of Reyataz with boceprevir resulted in lower exposure of Reyataz which may be associated with lower efficacy and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring for HIV suppression is warranted. The PL has been updated accordingly.
IAIN/0079	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	19/03/2012	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0070	Update of sections 4.2, 4.6 and 5.2 of the SmPC with pharmacokinetic and safety data from study AI424182 of ATV/RTV administered as part of HAART to HIV infected pregnant women. The PL was updated accordingly. In addition, section 4.6 of the SmPC is updated to include the most current information of ATV exposure during pregnancy. Finally, changes to sections 4.5, 4.7, 4.8, 5.1 of the SmPC, Annex II.B and patient leaflet have been made in line with the SmPC guideline (revision 2, September 2009) and QRD template version 7. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	22/11/2011	SmPC, Annex II and PL	Study AI424182 was a multi-center, open-label, prospective, single-arm study designed to determine which dosing regimen of ATV/RTV produces adequate drug exposure during pregnancy compared to drug exposure of HIV-infected subjects from historical data. On the basis of the pharmacokinetic data in the study AI424182 and consideration of other publicly available data, a dose adjustment for ATV/RTV is not recommended in pregnant women. However, during second and third trimesters of pregnancy, ATV/RTV 300/100 mg with may not provide sufficient exposure, especially when the activity of ATV or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring may be considered to ensure adequate exposure. For patients with concomitant use of TDF or an H2-receptor antagonist, an increased dose of ATV/RTV 400 mg/100 mg is recommended along with therapeutic drug monitoring where feasible to ensure adequate Cmin values. The combination of TDF, H2-receptor antagonist and ATV/RTV is not recommended in pregnancy. Since post-partum exposures are expected to be higher than normal for the first two months after delivery, additional monitoring for adverse reactions during this period would be advisable. No PK data in neonates beyond the cord blood concentrations and associated plasma protein binding at delivery were collected. With regards to efficacy, the

					efficacy of ATV/RTV as a prophylactic treatment in vertical transmission can not be determined due to the very small sample size enrolled in study AI424182. No new or unanticipated safety issues for the mothers and infants were observed. However, the limited sample size of the study mandates particular caution in the interpretation of the safety data, especially as regards the risk of hyperbilirubinemia in neonates.
IA/0078	A.7 - Administrative change - Deletion of manufacturing sites	28/10/2011	n/a		
II/0074	Update of sections 4.4 and 4.8 of the SmPC with Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome based on the review of the MAH safety database and the published literature. The PL has been amended accordingly. The list of local representatives 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	21/07/2011	24/08/2011	SmPC and PL	The MAH performed a cumulative search of their safety database including all spontaneous, literature, and clinical trial cases that were reported cumulatively to 12 February 2010 including ATV as a suspect or interacting drug (regardless of formulation or causality) and MedDRA preferred terms of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM). Following a request from the CHMP, the MAH also performed a cumulative review of drug rash with eosinophilia and systemic symptoms (DRESS) syndromes on their safety database on the period from 20 June 2003 to 10 February 2011. The CHMP concluded that, even if in some cases, confounding factors can be identified, the causal relationship of ATV in the occurrence of these severe skin reactions cannot be ruled out. Moreover, in some cases, the chronology is suggestive. Hence, section 4.4 and 4.8 of the SmPC were updated with SJS (frequency: rare), erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and DRESS syndrome (frequency:

					uncommon). The PL has been amended accordingly.
IB/0077/G	This was an application for a group of variations. C.I.7.a - Deletion of - a pharmaceutical form A.7 - Administrative change - Deletion of manufacturing sites	17/05/2011	n/a	SmPC, Annex II, Labelling and PL	To delete Reyataz Oral Powder (50 mg as the free base/1.5 g powder, EU/1/03/267/007),. Bristol-Myers Squibb, Meymac, France is the only approved manufacturing site for Reyataz Oral Powder in bottle for secondary packaging and quality control release testing in the EEA. Currently the MAH is unable to identify another site within the EEA to perform these activities for the Oral Powder in bottle. As a result the MAH proposes to delete this formulation. Reyataz Oral Powder in bottle has never been launched anywhere in the EEA, therefore, this deletion is not as a consequence of any safety concern and will not cause any public safety concern. To delete two registered manufacturing sites for Reyataz hard capsules as both manufacturing sites have ceased operation.
II/0075	Update of sections 4.3, 4.4 and 4.5 of the SmPC to reflect changes in the drug-drug interactions of ATV and drugs metabolised by CYP3A4, including PDE5 inhibitors, alfuzosin and salmeterol. The PL has been revised accordingly. Update of Annex IIB to delete the DDPS version number. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	24/03/2011	SmPC, Annex II and PL	Atazanavir is an inhibitor of CYP3A4 and UGT1A1. Coadministration of ATV and drugs primarily metabolized by CYP3A4 or UGT1A1 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic effects and its adverse effects. A literature search was conducted by the MAH on the effect of ATV/RTV on several drugs that are known CYP3A4 substrates, including alfuzosin, phosphodiesterase type 5 (PED5) inhibitors (sildenafil, tadalafil, and vardenafil), and salmeterol. After reviewing the available drug-drug interaction data, including the literature data, sections 4.3, 4.4 and 4.5 of the SmPC and section 2 of the PL were updated to reflect contraindications to use with alfuzosin

					and with sildenafil for PAH; warnings to use with PED5 inhibitors for erectile dysfunction and with salmeterol.
IA/0076	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 DD	04/03/2011	n/a		
IB/0072	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	22/09/2010	n/a	SmPC	Following the CHMP request dated 24 June 2010, the MAH amends section 4.5 "interaction with other medicinal products and other forms of interaction" of the SmPC to include the results of the drug interaction study of the effect of Atazanavir (ATV) on the pharmacokinectics of Raltegravir (RAL) as described in the ISentress (RAL) SmPC. The MAH also made minor linguistic amendments to the PIs in the other languages.
IA/0073/G	This was an application for a group of variations. 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/09/2010	n/a		
IB/0069/G	This was an application for a group of variations.	01/09/2010	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
IA/0071	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	11/08/2010	n/a	Annex II	
II/0057	Extension of Indication	22/04/2010	05/07/2010	SmPC, Annex II and PL	
II/0056	Update of section 4.5 of the SmPC based on the final study report for AI424360, evaluating the interaction between atazanavir/ritonavir and rifabutin (in fulfilment of follow-up measure 56.4). Update of section 4.4 following CHMP request to improve the wording on the co-administration of atazanavir/ritonavir with efavirenz. Update of the local representative for Cyprus in the PL. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	15/03/2010	SmPC and PL	Study AI424360 evaluating the exposure of rifabutin administered in an alternate regimen in combination with atazanavir and ritonavir in healthy volunteers showed that the rifabutin dose of 150 mg twice weekly provides satisfactory pharmacokinetic results. However, there are concerns of a potential risk for rifabutin resistance in treated patients leading to treatment failure and exacerbating the growing problem of Mycobacterium Tuberculosis (MTB) resistance. These concerns were mainly due to potential lower rifabutin exposure levels in HIV infected patients than those in healthy subjects as reported

					in the literature. The public health risk of Tuberculosis treatment failure and worsening MTB drug resistance outweigh the risks of possible greater rifabutin adverse events that may come with the three times weekly dosing. Furthermore, the risk of the toxicity can be mitigated through the closer monitoring for rifabutin- associated adverse reactions. Therefore, the current dose recommendation of 150 mg three times a week when co-administered with atazanavir/ritonavir was maintained. A statement was included recommending close clinical monitoring for rifabutin related adverse events and a further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated.
IA/0068/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details 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	12/03/2010	n/a	Annex II	
II/0067	Addition of an alternative manufacturer of the finished product (hard capsules). Quality changes	19/11/2009	25/11/2009		

II/0059	Update of sections 4.4 and 4.5 of the SmPC by including a dosing recommendation for oral contraceptives when co-administered with atazanavir/ritonavir based on a pharmacokinetic study in healthy volunteers in fulfilment of Clinical Follow-up Measure 071. Consequently, the PL was updated. In addition, the MAH took this opportunity to update contact details of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	20/11/2009	SmPC and PL	In a study in healthy female volunteers, atazanavir/ritonavir 300/100 mg once daily was given together with an oral contraceptive ("the Pill") that contained ethinyl estradiol and norgestimate. As a consequence, blood levels of the oestrogen component were reduced by approximately 20%, while the progestin was markedly increased (approx. 85%). Nevertheless, the study allowed the determination of a dosing recommendation for the co-administration of atazanavir/ritonavir and ethinyl estradiol/norgestimate in women who wish to use this method of contraception. However, adherence to the oral contraceptive regimen is key; this was therefore emphasised. In addition, the increased blood levels of the progestin component could lead to related side effects influencing compliance. Also, the dosing recommendation only applies to oral contraceptives containing ethinyl estradiol and norgestimate as other combinations have not been tested and should therefore be avoided.
II/0049	Update of sections 4.4 and 4.5 of the SPC based on an interaction study of atazanavir/ritonavir with the H2-receptor antagonist famotidine in HIV-infected patients further to the CHMP's request of July 2006 (follow-up measure 045.3). Consequently, the PL has been updated. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	Based on the results of two drug-drug interaction studies exploring the co-administration of atazanavir/ritonavir and famotidine with our without tenofovir in the therapeutic backbone (one in healthy volunteers, one in HIV-infected patients), the information on the interaction of Reyataz with the H2-recepter antagonist was updated to give the information that in patients not taking tenofovir, lower doses of famotidine do not require dose adjustment, while a dose increase of atazanavir/ritonavir could be considered when e.g. 40 mg famotidine is administered twice daily. However, in patients who are taking tenofovir, co-administration of atazanavir/ritonavir and a H2 receptor

					antagonist should be avoided, as this could result in sub-optimal atazanavir exposures. Nevertheless, if such a combination is judged unavoidable, close clinical monitoring is recommended. A dose increase of atazanavir/ritonavir may be considered but is still under evaluation.
II/0054	Update of sections 4.8 and 5.1 of the SPC based on the 96-week report for study AI424138, addressing follow-up measure 069. The MAH also responded to the CHMP conclusions on FUM 068 related to the re-formatting of section 5.1 of the SPC. Additionally, the MAH took the opportunity to correct minor typographical errors in the SPC. Update of Summary of Product Characteristics	23/04/2009	08/06/2009	SmPC	The 96 week data of AI424138 (also known as CASTLE) confirmed the observed non-inferiority of atazanavir/ritonavir in antiretroviral treatment naïve patients when compared to a lopinavir/ritonavir containing regimen (please also refer to the 48 week data assessment in the scientific conclusion for variation II/39). No new safety issues were identified. In addition, the MAH took this opportunity to provide information on the antiviral activity and resistance data in vitro, as well as on de novo mutations in patients failing on atazanavir/ritonavir in more detail. For these details, please also see the Scientific Discussion Reyataz H-C-494-II-54.
IB/0066	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	05/06/2009	n/a		
IB/0065	IB_10_Minor change in the manufacturing process of the active substance	05/06/2009	n/a		
IB/0064	IB_10_Minor change in the manufacturing process of the active substance IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	05/06/2009	n/a		
II/0063	Update of sections 4.2, 4.4 and 5.2 of the SPC by including information and a warning regarding	23/04/2009	15/05/2009	SmPC and PL	Study AI424-105 was performed in order to evaluate the safety and pharmacokinetics of atazanavir in subjects with

	patients with renal impairment receiving haemodialysis following the CHMP conclusions dated 22 January 2009 on Follow-up Measure FU2 038.2 (data analysis of study AI424-105, a study in subjects with renal impairment). Consequently, the PL was updated. Paediatrics to validate Update of Summary of Product Characteristics and Package Leaflet				normal renal function or severe renal impairment with or without haemodialysis. The study did not assess the impact of atazanavir/ritonavir on these patients. Patients with severe renal impairment without haemodialysis showed comparable exposure to those with normal kidney function, while patients with severe renal impairment with haemodialysis presented lower plasma atazanavir exposure. Atazanavir was not markedly cleared from plasma during haemodialysis. The mechanism of the trend in reduction in atazanavir exposures in patients managed with haemodialysis relative to patients with normal renal function is not clear. In the absence of data on atazanavir/ritonavir on patients managed with haemodialysis and without any clear mechanism for the observed lower exposure in these patients, the CHMP concluded that atazanavir/ritonavir is not recommended in these patients.
IA/0062	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	18/03/2009	n/a	Annex II and PL	
IA/0061	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	18/03/2009	n/a		
II/0055	Update of Detailed Description of the Pharmacovigilance System (DDPS) Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	26/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version

					number of the agreed DDPS.
R/0052	Renewal of the marketing authorisation.	20/11/2008	06/02/2009	SmPC, Annex II, Labelling and PL	Based on the CHMP 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 Reyataz continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Reyataz with unlimited validity.
IA/0060	IA_09_Deletion of manufacturing site	06/02/2009	n/a		
II/0050	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 atazanavir given with concomitant low-dose ritonavir. The MAH also took the opportunity to correct a minor typing mistake in the English Package Leaflet for the 300 mg hard capsules. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	27/10/2008	SmPC and PL	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.
IA/0053	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/09/2008	n/a		

IA/0051	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	27/08/2008	n/a		
IA/0048	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	28/07/2008	28/07/2008	SmPC, Labelling and PL	
S/0047	Annual reassessment Fourth annual reassessment	24/04/2008	25/07/2008	SmPC, Annex II and PL	In view of the submitted efficacy and safety data, the CHMP concluded that the benefit risk balance of ritonavir-boosted atazanavir in antiretroviral experienced adult patients remains positive. As all remaining Specific Obligations were fulfilled, the CHMP agreed that exceptional circumstances should be lifted.
II/0039	Extension of the therapeutic indication of to include antiretroviral treatment naïve patients. In addition, the MAH took this opportunity to update contact details of local representatives in the PL. Extension of Indication	24/04/2008	20/06/2008	SmPC and PL	Please refer to the scientific conclusions: Reyataz-H-494-II-39-AR
II/0034	Update of sections 4.4, 4.5 and 4.8 of the SPC following the CHMP's assessment of PSUR 5 in April 2007. The MAH took this opportunity to update section 4.8 to reflect version 8.2 of the MedDRA system Order Class database. Consequently, the PL was updated as well. In addition, the MAH took this opportunity to update the PL with contact details for Denmark and	24/04/2008	20/06/2008	SmPC and PL	Following cumulative reviews for both gall bladder disorder and kidney stones in patients treated with atazanavir, a possible link between these adverse reactions and atazanavir therapy could not be excluded. Therefore, the SPC was updated with this information. In addition, the interaction with voriconazole based on available literature data and extrapolated to the current atazanavir/ritonavir twice daily regimen was added to the Product Information as an interaction that might be clinically relevant. The

	Romania. Update of Summary of Product Characteristics and Package Leaflet				opportunity was taken to clarify the existing paragraph on the interaction of atazanavir/ritonavir with azole antifungals in section 4.5. The PL was updated in accordance.
II/0031	Update of sections 4.4 and 4.5 of the SPC based on two drug-drug interaction studies with the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz and atazanavir/ritonavir. Consequently, the PL is updated. The MAH took this opportunity to reformat section 4.5 of the SPC to a tabular format. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	Interaction data from a study exploring the co-administration of the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) nevirapine showed that the co-administration of nevirapine with atazanavir/ritonavir significantly decreased the exposure of atazanavir, which could alter the anti-retroviral efficacy of the treatment. Despite an increase of the atazanavir dosage from 300 mg to 400 mg, the interaction could not be overcome. Therefore, the co-administration of nevirapine with atazanavir/ritonavir is not recommended. Interaction studies in relation to the interaction of another NNRTI, efavirenz, showed similar effects (i.e. an under-exposure of atazanavir). However, increases in the dosage to 400 mg atazanavir and 200 mg ritonavir could potentially overcome this effect. Nevertheless, due to the potential for inter-patient variability and taking into consideration that this dose recommendation was derived from extrapolation of data in healthy volunteers, the combination should only be used if deemed unavoidable and then only under close clinical monitoring.
II/0046	Update of section 4.5 of the SPC with information on the interaction of medicinal products used in the treatment of opioid dependency (buprenorphine and methadone) with atazanavir/ritonavir, as requested by the CHMP. Consequently, the Package Leaflet is updated as well.	19/03/2008	21/04/2008	SmPC and PL	In a pharmacokinetic (PK) interaction study there was no significant effect on methadone PK parameters when methadone was co-administered with atazanavir 400 mg. The CHMP deemed that a PK study with atazanavir boosted with ritonavir to overcome the limitation of the study with unboosted atazanavir was not necessary, given that some

	Update of Summary of Product Characteristics and Package Leaflet				data has showed no significant effect of low-dose ritonavir on methadone metabolism and that exposure to methadone is monitored in clinical practice. Overall the CHMP recommends no dose adjustment if methadone is co-administered with atazanavir/ritonavir. Published data have shown an increase in buprenorphine and in norbuprenorphine (the active metabolite) in case of co-administration of buprenorphine with atazanavir/ritonavir. Therefore the CHMP recommends clinical monitoring for sedation and cognitive effects when buprenorphine and atazanavir/ritonavir are co-administered and that a dose reduction in buprenorphine may be considered.
X/0033	The MAH applied for an additional strength of 300 mg capsules. Annex I_2.(c) Change or addition of a new strength/potency	21/02/2008	17/04/2008	SmPC, Labelling and PL	The MAH applied for an additional strength of 300 mg atazanavir capsules. Reyataz is already approved and available in three commercial strengths; 100 mg, 150 mg and 200 mg capsules of atazanavir. This new strength will allow providing the patients with a one-unit daily dose. The 300 mg capsule is obtained from the same formulation as the other existing strengths and by varying the capsule fill weight. The strengths can be differentiated by the size, colour and imprinting of the capsules. Based on the results from the bioequivalence study, the 300 mg Reyataz capsules can be considered bioequivalent to two 150 mg capsules.
II/0044	Change(s) to the manufacturing process for the active substance	21/02/2008	27/02/2008		
IA/0045	IA_22_a_Submission of TSE Ph. Eur. certificate for	10/01/2008	n/a		

	exc. - Approved/new manufacturer				
IB/0037	IB_38_c_Change in test procedure of finished product - other changes	08/01/2008	n/a		
IB/0040	IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	20/12/2007	n/a		
II/0032	Update of sections 4.2, 4.3, 4.4 and 4.5 of the SPC with data regarding the interaction of atazanavir/ritonavir with proton pump inhibitors. Consequently, the PL is updated. In addition, the MAH took this opportunity to harmonise the expression of an excipient in section 6.1 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	15/11/2007	19/12/2007	SmPC and PL	The co-administration of omeprazole 20 mg once daily with atazanavir/ritonavir was studied in healthy volunteers. An increased dose of atazanavir/ritonavir (400/100 mg once daily instead of the approved 300/100 mg once daily regimen) resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir/ritonavir 300/100 mg once daily without omeprazole. This decrease was not compensated when the increased dose of atazanavir/ritonavir was temporally separated from the dose of omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. In a previous pharmacokinetic study performed with omeprazole 40 mg once daily, the decrease observed in atazanavir exposure was about 75% and therefore the co-administration of proton pump inhibitors with atazanavir/ritonavir was contra-indicated. Although the decrease in atazanavir exposure observed with omeprazole 20 mg is less important and no longer warrants an absolute contra-indication, it is still considered a substantial decrease which might negatively impact the efficacy of atazanavir. Therefore, the CHMP recommended limiting this co-

					administration to patients in whom it cannot be avoided. In these instances, close clinical monitoring is required.
IA/0043	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	17/12/2007	n/a		
IA/0042	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	17/12/2007	n/a		
IA/0041	IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	17/12/2007	n/a		
IB/0036	IB_30_b_Change in supplier of packaging components - replacement/addition	06/12/2007	n/a		
IA/0038	IA_37_a_Change in the specification of the finished product - tightening of specification limits	28/11/2007	n/a		
IA/0035	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	06/08/2007	n/a		
S/0029	Third annual reassessment	24/05/2007	20/07/2007	Annex II	In view of the submitted efficacy and safety data, the CHMP concluded that the benefit risk balance of ritonavir-boosted atazanavir in antiretroviral experienced adult patients remains positive. As there are still remaining Specific Obligations, the CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances.
IA/0030	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	05/06/2007	n/a		

II/0027	Update of section 4.4 of the SPC to complete the current warning as regards fat redistribution and metabolic disorders by underlining the need for an adequate clinical management of dyslipidaemia. This follows a request from the CHMP in December 2006. Update of Summary of Product Characteristics	22/03/2007	26/04/2007	SmPC	Atazanavir had shown during studies conducted for its development a more favourable lipid profile than other antiretroviral agents. Therefore, a study in order to demonstrate a clinical benefit in terms of reduced cardiovascular morbidity/mortality had been requested when it was first approved in the EU. Statistical modelling showed that such a prospective study would be non-feasible, as the number of needed patients (at least 3500) and years (at least 8) are unrealistic. The CHMP considered that the therapeutic management of HIV-infected patients should be primarily driven by the antiretroviral efficacy of the used agents. A statement was therefore introduced to warn physicians that the observed biological impact of atazanavir on lipid levels could not be translated into a clinical benefit and that therapeutic management of lipid disorders should be based on current standard guidelines for the management of dyslipidaemia.
II/0022	Update of sections 4.3 and 4.5 of the SPC with information on the concomitant use of ritonavir boosted atazanavir with triazolam and midazolam based on information available in the public domain. Consequentially, section 2 of the Package Leaflet was updated as well. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	27/03/2007	SmPC and PL	Similar to other protease inhibitors, atazanavir dosed with ritonavir inhibits CYP3A. Collectively, the data based on a literature review demonstrate that exposure of triazolam and midazolam is increased when co-administered with known CYP3A inhibitors. Therefore, the co-administration with atazanavir/ritonavir may result in substantially increased exposures of these benzodiazepines as well. Triazolam and midazolam administered orally should not be co-administered with atazanavir/ritonavir due to the potential increase of therapeutic and adverse effects of these benzodiazepines. As increased exposures were lower with parenteral midazolam, less than one half the magnitude compared to oral midazolam, and use of

					injectable midazolam would occur in a hospital or clinic setting in anaesthesia parenteral midazolam and atazanavir/ritonavir may be co-administered with caution.
IA/0028	IA_13_a_Change in test proc. for active substance - minor change	20/03/2007	n/a		
II/0025	Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Section 6 of the PL was updated with the local representatives in Bulgaria, Romania, Estonia, Greece, Iceland, Latvia and Lithuania. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	17/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
IB/0023	IB_10_Minor change in the manufacturing process of the active substance	11/01/2007	n/a		
IA/0026	IA_13_a_Change in test proc. for active substance - minor change	15/12/2006	n/a		
IA/0024	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	06/11/2006	n/a		

S/0021	Second annual reassessment	01/06/2006	28/07/2006	SmPC, Annex II, Labelling and PL	In view of the submitted efficacy and safety data, the CHMP concluded that the benefit risk balance of ritonavir-boosted atazanavir in antiretroviral experienced adult patients remains positive. Long-term efficacy and safety data of the boosted atazanavir regimen was provided with the 96-weeks report for the pivotal study -045. Furthermore, study -138 comparing ritonavir boosted atazanavir versus ritonavir boosted lopinavir in antiretroviral naïve patients is awaited to properly assess the benefit risk balance of the medicinal product in first line therapy and its use within once daily triple regimen. With respect to safety issues, bilirubin disorders represent the most prominent aspect of the safety profile of atazanavir when compared to other PIs. However, atazanavir seems to be a lower dyslipidaemia inducer than other PIs (shown for nelfinavir, lopinavir/ritonavir) and efavirenz. Nevertheless, it appears not feasible to demonstrate whether this biological effect can be translated into a positive clinical impact (reduction of cardiac morbidity/mortality risk). Therefore, the short-term safety data available on the effect of atazanavir on the lipid profile should not be regarded as sufficiently robust to deviate from the standard guidelines for management of dyslipidaemia. As there are still remaining Specific Obligations, the CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances.

II/0017	Update of section 4.5 of the SPC with the interaction data on atazanavir and tenofovir. Also, update of section 4.8 with respect to diabetes mellitus and hyperglycaemia in post-marketing experience. These updates follow the CHMP's assessment of the data presented in the PSUR covering the period from 20 December 2004 to 19 June 2005 and the MAH's cumulative search of the company safety database for all spontaneous reports, literature and all related clinical study reports from the IBD (International birth date) 20 June 2003. Update of Summary of Product Characteristics	01/06/2006	06/07/2006	SmPC	Results of study AI424113, combined with other existing data previously submitted (Puzzle II) support amendments to section 4.5 of the SPC with a wording about atazanavir increasing tenofovir concentrations and that the mechanism of this interaction is unknown. Additionally, the post marketing reports of renal events with regimens containing tenofovir also support this amendment as well as justifying the addition of the information that higher tenofovir concentrations may potentate tenofovir associated adverse effects, including renal disorders. Therefore, section 4.5 was updated with this additional information. Furthermore, information provided in the 4th PSUR confirmed that atazanavir could be associated with diabetes mellitus as well as hyperglycaemia. Even though multiple confounding factors were present and diabetes mellitus and hyperglycaemia are listed as a class labelling in section 4.4 these undesirable effects were added in section 4.8 of the SPC.
IA/0020	IA_06_a_Change in ATC code: Medicinal products for human use	28/02/2006	n/a	SmPC	
IA/0019	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	16/02/2006	n/a		
IA/0018	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	08/02/2006	n/a	Annex II and PL	

II/0014	Further to the assessment of a Specific Obligations on the cardiotoxic potential of atazanavir, sections 4.4 and 5.3 of the SPC were updated. In the Package Leaflet details of local representatives were updated. Update of Summary of Product Characteristics and Package Leaflet	14/12/2005	25/01/2006	SmPC and PL	A precautionary statement about atazanavir and its co administration with medinical products that have the potential to increase the QT interval as well as its use in patients with pre-exisiting riks factors such as bradycardia, long congenital QT and/or electrolyte imbalances was added to the "Special Warnings and Precautions for Use" section of the SPC. This follows the assessment of in vitro data that showed a signal of prolonged re-polarisation in the human cardiac potassium channel and Rabbit Purkinje fiber studies at supra therapeutic concentrations.
IB/0015	IB_38_c_Change in test procedure of finished product - other changes	09/01/2006	n/a		
IA/0016	IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	12/12/2005	n/a		
II/0011	Update of sections 4.4 and 4.5 of the SPC to include interaction information regarding the H2 antagonist famotidine. Update of Summary of Product Characteristics	13/10/2005	17/11/2005	SmPC	Both Proton pump inhibitors (PPI) and H2 antagonists induce a decrease in pharmacokinetic exposure of atazanavir. However, the magnitude of the effect is much more marked with PPI. Such an effect is not compensated with the addition of an acidic beverage such as Cola. Moreover, the explored dose adjustment of atazanavir/ritonavir from 300/100 to 400/100 is not considered appropriate in the context of these co-administrations. Therefore, section 4.5 of the SPC was updated to reflect the knowledge on concomitant administration of Reyataz and famotidine (H2 antagonist). The mechanism behind the decreased oral bioavailability of atazanavir when co-administered with omeprazole seems

					to be decreased solubility of atazanavir at increased gastric pH. The solubility of atazanavir, and hence absorption, is likely to decrease substantially when gastric pH reaches above 4. Therefore a more general warning was included in section 4.4 of the SPC, to inform prescribers that absorption of atazanavir is expected to be substantially reduced in situations where gastric pH is increased, irrespective of cause, and that atazanavir may not be a suitable treatment option under these circumstances.
II/0010	Update of sections 4.1, 4.8 and 5.1 of the SPC to include 96-week safety and efficacy data available from a pivotal clinical study. Update of Summary of Product Characteristics	13/10/2005	17/11/2005	SmPC	This was a multinational, open label study performed in a limited sample size of moderately experienced patients. The safety results of the study were a slightly increased frequency of bilirubin elevations (53% instead of previously 49 %), a confirmation of the frequency of lipodystrophy and updated data on the lipid profile changes after long-term treatment. Regarding the efficacy outcome, the durability of antiviral activity as well as a non-inferiority as regards to treatment with lopinavir/ritonavir could be confirmed.
S/0006	First annual reassessment.	23/06/2005	16/09/2005	Annex II	The CHMP reviewed the evidence of compliance with the specific obligations (SOBs) and re-assessed the benefit risk balance of the medicinal product. Some SOBs and follow-up measures remain unresolved. Therefore, the CHMP agreed that the Marketing Authorisation remains under exceptional circumstances. Taking into consideration all available data on quality, efficacy and safety, the overall benefit/risk balance of Reyataz has not changed and remains favourable.

IA/0013	IA_01_Change in the name and/or address of the marketing authorisation holder	06/09/2005	n/a	SmPC, Labelling and PL	
IB/0012	IB_38_c_Change in test procedure of finished product - other changes	02/09/2005	n/a		
II/0009	Update of sections 4.4 and 4.5 of the SPC and point 2 of the PL with the class labelling text on "fluticasone" following the CHMP Assessment Report on the "Interaction with ritonavir boosted protease inhibitors and fluticasone" dated 26 May 2005. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	24/08/2005	SmPC and PL	The MAH implements the class labelling on the fluticasone propionate- ritonavir interaction. This interaction is supported by the results of one multiple-dose crossover design clinical study in healthy subjects, conducted by GSK in July- October 2002. This study aimed at evaluating the effects of several CYP3A4 inhibitors, including ritonavir, ketoconazole and erythromycin on systemic concentrations of fluticasone after nasal inhalation.
IA/0008	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	30/06/2005	n/a		
IA/0007	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	30/06/2005	n/a		
II/0005	To amend sections 4.4 and 4.5 of the SPC and section 2 of the PL to include the warning on the atazanavir/ritonavir drug interaction with a proton pump inhibitor, omeprazole. Update of Summary of Product Characteristics and Package Leaflet	20/01/2005	21/02/2005	SmPC and PL	Variation based on the results of interaction the study AI424115: This is a randomised, open-label, multiple-dose trial to evaluate the effect of omeprazole on the pharmacokinetics of a boosted atazanavir regimen in 48 healthy subjects (ages of 18-50 years with a BMI between 18 to 30kg/m2). The primary objective of the study was to assess the comparability of the steady-state pharmacokinetics of ATV/RTV at 300/100 mg with 8 ounces of cola and ATV/RTV at 400/100mg, both co-administered with omeprazole relative to ATV/RTV at 300/100 mg alone.

					Results showed an important decrease of atazanavir exposure (76% and 78% decrease of atazanavir AUC and Cmin respectively). Neither the dose increase of atazanavir (in combination with 100 mg ritonavir) from 300 mg to 400mg nor the co-administration with cola could compensate for such a decrease induced by the omeprazole co-administration. Therefore, the CHMP recommended the contra-indication of proton pump inhibitors with Reyataz. Ritonavir pharmacokinetic parameters were also decreased but to a lesser extent. The mechanism of this interaction as well as the interaction between atazanavir and H2 inhibitors is further explored.
II/0004	To update section 4.4 and 4.8 of the SPC and section 2 of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics and Labelling	18/11/2004	21/12/2004	SmPC and PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases, the inflammatory reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/ diagnosed. If diagnosed prior to institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infections and Pneumocystis carinii pneumonia. An additional reason for treating the OI and the HIV-infection sequentially, is the great risk of adverse events (toxicity or lack of effect) due to drug interactions. in conclusion, in most cases, the clinical consequences of the awakening immune system in patients starting ART cannot be prevented. Therefore, early

					recognition and diagnosis of these inflammatory reactions are important in the clinical handling of the patient. The description and the guidelines for treatment of the numerous clinical conditions potentially arising in association with the reactivation of the immune system in HIV-infected patients are given in the textbooks of infectious diseases. However, as the clinical conditions associated with the reactivation of the immune system may constitute a threat to the patient, a reminder of the phenomenon is deemed of value and has been included in the SPC and PL of all antiretroviral medicinal products.
II/0001	Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	19/07/2004	SmPC, Labelling and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2004	n/a	Labelling and PL	