ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
REYATAZ 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REYATAZ 200 mg hard capsules

Each capsule contains 200 mg of atazanavir (as sulphate).

Excipient with known effect: 109.57 mg of lactose per capsule.

REYATAZ 300 mg hard capsules

Each capsule contains 300 mg of atazanavir (as sulphate).

Excipient with known effect: 164.36 mg of lactose per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

REYATAZ 200 mg hard capsules

Opaque blue capsule printed with white ink, with "BMS 200 mg" on one half and with "3631" on the other half.

REYATAZ 300 mg hard capsules

Opaque red and blue capsule printed with white ink, with "BMS 300 mg" on one half and with "3622" on the other half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV-1-infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products (see section 4.2).

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations).

The choice of REYATAZ in treatment-experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults
The recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1). (See also section 4.4 Withdrawal of ritonavir only under restrictive conditions).

Paediatric patients (6 years to less than 18 years of age and weighing at least 15 kg)
The dose of atazanavir capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.

Table 1: Dose for paediatric patients (6 years to less than 18 years of age and weighing at least 15 kg) for REYATAZ capsules with ritonavir

Body Weight (kg)	REYATAZ once daily dose	ritonavir once daily dose[a]
15 to less than 35	200 mg	100 mg
at least 35	300 mg	100 mg

[a] Ritonavir capsules, tablets or oral solution.

Paediatric patients (at least 3 months of age and weighing at least 5 kg): REYATAZ oral powder is available for paediatric patients at least 3 months of age and weighing at least 5 kg (see Summary of Product Characteristics for REYATAZ oral powder). Switching to REYATAZ capsules from REYATAZ oral powder is encouraged as soon as patients are able to consistently swallow capsules.

When transitioning between formulations, a change in dose may be needed. Consult the dosing table for the specific formulation (see Summary of Product Characteristics for REYATAZ oral powder).

Special populations

Renal impairment
No dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4, and 5.2).

Hepatic impairment
REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ with ritonavir must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

In case of withdrawal of ritonavir from the initial recommended ritonavir-boosted regimen (see section 4.4), unboosted REYATAZ could be maintained in patients with mild hepatic impairment at a dose of 400 mg, and in patients with moderate hepatic impairment with a reduced dose of 300 mg once daily with food (see section 5.2). Unboosted REYATAZ must not be used in patients with severe hepatic impairment.

Pregnancy and Postpartum
During the second and third trimesters of pregnancy:
REYATAZ 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir 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 (TDM) may be considered to ensure adequate exposure.

The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to reduce its exposure (e.g., tenofovir disoproxil or H_2-receptor antagonists).

- If tenofovir disoproxil or an H_2-receptor antagonist is needed, a dose increase to REYATAZ 400 mg with ritonavir 100 mg with TDM may be considered (see sections 4.6 and 5.2).
- It is not recommended to use REYATAZ with ritonavir for pregnant patients who are receiving both tenofovir disoproxil and an H_2-receptor antagonist.

(See section 4.4 Withdrawal of ritonavir only under restrictive conditions).

During postpartum:
Following a possible decrease in atazanavir exposure during the second and third trimester, atazanavir exposures might increase during the first two months after delivery (see section 5.2). Therefore, postpartum patients should be closely monitored for adverse reactions.

- During this time, postpartum patients should follow the same dose recommendation as for non-pregnant patients, including those for co-administration of medicinal products known to affect atazanavir exposure (see section 4.5).

Paediatric patients (less than 3 months of age)
REYATAZ should not be used in children less than 3 months because of safety concerns especially taking into account the potential risk of kernicterus.

Method of administration:

For oral use. The capsules should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

REYATAZ is contraindicated in patients with severe hepatic insufficiency (see sections 4.2, 4.4 and 5.2). REYATAZ with ritonavir is contraindicated in patients with moderate hepatic insufficiency (see sections 4.2, 4.4, and 5.2).

Co-administration with simvastatin or lovastatin (see section 4.5).

Combination of the PDE5 inhibitor sildenafil when used for the treatment of pulmonary arterial hypertension (PAH) only (see section 4.5). For co-administration of sildenafil for the treatment of erectile dysfunction see sections 4.4 and 4.5.

Co-administration with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), lomitapide, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

Co-administration with medicinal products that are strong inducers of CYP3A4 due to the potential for loss of therapeutic effect and development of possible resistance (e.g., rifampicin, St. John's wort, apalutamide, encorafenib, ivosidenib, carbamazepine, phenobarbital and phenytoin) (see section 4.5).

Co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination (see section 4.5).

Co-administration with glecaprevir/pibrentasvir fixed-dose combination (see section 4.5).

4.4 Special warnings and precautions for use

Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with coexisting conditions

Hepatic impairment: Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal impairment: No dosage adjustment is needed in patients with renal impairment. However, REYATAZ is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

QT prolongation: Dose-related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

Haemophiliac patients: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to the disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, REYATAZ with ritonavir has been shown to induce dyslipidaemia to a lesser extent than lopinavir with ritonavir in either treatment-naïve patients (Study 138) or treatment-experienced patients (Study 045), (see section 5.1).

Hyperbilirubinaemia

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be evaluated for alternative aetiologies. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these medicinal products is not recommended (see section 4.5).

Withdrawal of ritonavir only under restrictive conditions

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
- viral strains not harbouring HIV resistance associated mutations (RAMs) to current regimen.

REYATAZ given without ritonavir should not be considered in patients treated with a backbone regimen containing tenofovir disoproxil and with other concomitant medications that reduce atazanavir bioavailability (see section 4.5 In case of withdrawal of ritonavir from the recommended atazanavir boosted regimen) or in case of perceived challenging compliance.

REYATAZ given without ritonavir should not be used in pregnant patients given that it could result in suboptimal exposure of particular concern for the mother infection and vertical transmission.

Cholelithiasis

Cholelithiasis has been reported in patients receiving REYATAZ (see section 4.8). Some patients required hospitalisation for additional management and some had complications. If signs or symptoms of cholelithiasis occur, temporary interruption or discontinuation of treatment may be considered.

Chronic kidney disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown 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 (see section 4.8).

Nephrolithiasis

Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). Some patients required hospitalisation for additional management and some had complications. In some cases, nephrolithiasis has been associated with acute renal failure or renal insufficiency. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Rash and associated syndromes

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in patients receiving REYATAZ. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. REYATAZ should be discontinued if severe rash develops.

The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of REYATAZ, REYATAZ may not be restarted.

Interactions with other medicinal products

The combination of REYATAZ with atorvastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5). If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ and medicinal products that induce CYP3A4 is not recommended (see section 4.5).

PDE5 inhibitors used for the treatment of erectile dysfunction: particular caution should be used when prescribing PDE5 inhibitors (sildenafil, tadalafil, or vardenafil) for the treatment of erectile dysfunction in patients receiving REYATAZ. Co-administration of REYATAZ with these medicinal products is expected to substantially increase their concentrations and may result in PDE5-associated adverse reactions such as hypotension, visual changes, and priapism (see section 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended, unless an assessment of the benefit/risk justifies the use of voriconazole.

In the majority of patients, a reduction in both voriconazole and atazanavir exposures are expected. In a small number of patients without a functional CYP2C19 allele, significantly increased voriconazole exposures are expected (see section 4.5).

Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Concomitant use of salmeterol and REYATAZ may result in increased cardiovascular adverse events associated with salmeterol. Co-administration of salmeterol and REYATAZ is not recommended (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate or norethindrone has not been studied, and therefore should be avoided (see section 4.5).

Paediatric population

Safety
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

Efficacy
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, lomitapide, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

Co-administration of REYATAZ with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination is contraindicated because of the increase in grazoprevir and elbasvir plasma concentrations and potential for the increase in risk of ALT elevations associated with increased grazoprevir concentrations (see section 4.3). Co-administration of REYATAZ with glecaprevir/pibrentasvir fixed-dose combination is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecapreir and pibrentasvir plasma concentrations (see section 4.3).

Other interactions
Interactions between atazanavir and other medicinal products are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔"). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the recommended regimen of atazanavir (see section 4.4).

If withdrawal of ritonavir is medically warranted under restrictive conditions (see section 4.4), special attention should be given to atazanavir interactions that may differ in the absence of ritonavir (see information below Table 2).

Interactions between atazanavir and other medicinal products, including those for which co-administration is contraindicated, are listed in the table below:

Table 2: Interactions between REYATAZ and other medicinal products

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
ANTI-HCV AGENTS		
Grazoprevir 200 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily)	Atazanavir AUC: ↑43% (↑30% ↑57%) Atazanavir C_{max}: ↑12% (↑1% ↑24%) Atazanavir C_{min}: ↑23% (↑13% ↑134%) Grazoprevir AUC: ↑958% (↑678% ↑1 339%) Grazoprevir C_{max}: ↑524% (↑342% ↑781%) Grazoprevir C_{min}: ↑1 064% (↑696% ↑1 602%) Grazoprevir concentrations were greatly increased when co-administered with atazanavir/ritonavir.	Co-administration of REYATAZ and elbasvir/grazoprevir is contraindicated because of a significant increase in grazoprevir plasma concentrations and an associated potential increase in the risk of ALT elevations (see section 4.3).
Elbasvir 50 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily)	Atazanavir AUC: ↑7% (↓2% ↑17%) Atazanavir C_{max}: ↑2% (↓4% ↑8%) Atazanavir C_{min}: ↑15% (↑2% ↑29%) Elbasvir AUC: ↑376% (↑307% ↑456%) Elbasvir C_{max}: ↑315% (↑246% ↑397%) Elbasvir C_{min}: ↑545% (↑451% ↑654%) Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg single dose* (atazanavir 300 mg/ritonavir 100 mg once daily)	Sofosbuvir AUC: ↑40% (↑25% ↑57%) Sofosbuvir C_{max}:↑29% (↑9% ↑52%) Velpatasvir AUC: ↑93% (↑58% ↑136%) Velpatasvir C_{max}: ↑29% (↑7% ↑56%) Voxilaprevir AUC: ↑331% (↑276% ↑393%) Voxilaprevir C_{max}: ↑342% (↑265% ↑435%) *Lack of pharmacokinetics interaction bounds 70-143% Effect on atazanavir and ritonavir exposure has not been studied. Expected: ↔ Atazanavir ↔ Ritonavir The mechanism of interaction between REYATAZ/ritonavir and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, P-gp, and CYP3A.	Co-administration of REYATAZ with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Co-administration of REYATAZ with voxilaprevir-containing regimens is not recommended.
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily*)	Glecaprevir AUC: ↑553% (↑424% ↑714%) Glecaprevir C_{max}: ↑306% (↑215% ↑423%) Glecaprevir C_{min}: ↑1 330% (↑885% ↑1 970%) Pibrentasvir AUC: ↑64% (↑48% ↑82%) Pibrentasvir C_{max}: ↑29% (↑15% ↑45%) Pibrentasvir C_{min}: ↑129% (↑95% ↑168%) *Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.	Co-administration of REYATAZ with glecaprevir/pibrentasvir is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3)
ANTIPLATELETS		
Ticagrelor	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of REYATAZ with ticagrelor is not recommended due to potential increase in the antiplatelet activity of ticagrelor.
Clopidogrel	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and or/ritonavir.	Co-administration with clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
Prasugrel	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and or/ritonavir.	No dose adjustment is needed when prasugrel is co-administered with REYATAZ (with or without ritonavir).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTI-RETROVIRALS		
Protease inhibitors: The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.		
Ritonavir 100 mg once daily (atazanavir 300 mg once daily) Studies conducted in HIV-infected patients.	Atazanavir AUC: ↑250% (↑144% ↑403%)* Atazanavir C_{max}: ↑120% (↑56% ↑211%)* Atazanavir C_{min}: ↑713% (↑359% ↑1 339%)* *In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n = 33) was compared to atazanavir 400 mg without ritonavir (n = 28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.	Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Co-administration of REYATAZ and indinavir is not recommended (see section 4.4).
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine 150 mg twice daily + zidovudine 300 mg twice daily (atazanavir 400 mg once daily)	No significant effect on lamivudine and zidovudine concentrations was observed.	Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of these medicinal products and REYATAZ is not expected to significantly alter the exposure of the co-administered medicinal products.
Abacavir	The co-administration of abacavir and REYATAZ is not expected to significantly alter the exposure of abacavir.	
Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)	Atazanavir, simultaneous administration with ddI+d4T (fasted) Atazanavir AUC: ↓87% (↓92% ↓79%) Atazanavir C_{max}: ↓89% (↓94% ↓82%) Atazanavir C_{min}: ↓84% (↓90% ↓73%) Atazanavir, dosed 1 hr after ddI+d4T (fasted) Atazanavir AUC: ↔3% (↓36% ↑67%) Atazanavir C_{max}: ↑12% (↓33% ↑18%) Atazanavir C_{min}: ↔3% (↓39% ↑73%) Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.	Didanosine should be taken at the fasted state 2 hours after REYATAZ taken with food. The co-administration of stavudine with REYATAZ is not expected to significantly alter the exposure of stavudine.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Didanosine (with food) Didanosine AUC: ↓34% (↓41% ↓27%) Didanosine C_{max}: ↓38% (↓48% ↓26%) Didanosine C_{min}: ↑25% (↓8% ↑69%) No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.	
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil. Studies conducted in HIV-infected patients	Atazanavir AUC: ↓22% (↓35% ↓6%) * Atazanavir C_{max}: ↓16% (↓30% ↔0%) * Atazanavir C_{min}: ↓23% (↓43% ↑2%) * * In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir disoproxil fumarate 300 mg (n = 39) was compared to atazanavir/ritonavir 300/100 mg (n = 33). The efficacy of REYATAZ/ritonavir in combination with tenofovir disoproxil fumarate in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naïve patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir disoproxil fumarate is unknown.	When co-administered with tenofovir disoproxil fumarate, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir disoproxil fumarate 300 mg (all as a single dose with food).
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil.	Tenofovir disoproxil fumarate AUC: ↑37% (↑30% ↑45%) Tenofovir disoproxil fumarate C_{max}: ↑34% (↑20% ↑51%) Tenofovir disoproxil fumarate C_{min}: ↑29% (↑21% ↑36%)	Patients should be closely monitored for tenofovir disoproxil fumarate-associated adverse reactions, including renal disorders.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (pm): all administered with food Atazanavir AUC: ↔0%(↓9% ↑10%)* Atazanavir C_{max}: ↑17%(↑8% ↑27%)* Atazanavir C_{min}: ↓42%(↓51% ↓31%)*	Co-administration of efavirenz and REYATAZ is not recommended (see section 4.4).
Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 200 mg once daily)	Atazanavir (pm): all administered with food Atazanavir AUC: ↔6% (↓10% ↑26%)*/** Atazanavir C_{max}: ↔9% (↓5% ↑26%)*/** Atazanavir C_{min}: ↔12% (↓16% ↑49%)*/** *When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction. **Based on historical comparison.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Nevirapine 200 mg twice daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily) Study conducted in HIV-infected patients.	Nevirapine AUC: ↑26% (↑17% ↑36%) Nevirapine C_{max}: ↑21% (↑11% ↑32%) Nevirapine C_{min}: ↑35% (↑25% ↑47%) Atazanavir AUC: ↓19% (↓35% ↑2%)* Atazanavir C_{max}: ↔2% (↓15% ↑24%)* Atazanavir C_{min}: ↓59% (↓73% ↓40%)* *When compared to REYATAZ 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction.	Co-administration of nevirapine and REYATAZ is not recommended (see section 4.4).
Integrase Inhibitors		
Raltegravir 400 mg twice daily (atazanavir/ritonavir)	Raltegravir AUC: ↑41% Raltegravir C_{max}: ↑24% Raltegravir C_{12hr}: ↑77% The mechanism is UGT1A1 inhibition.	No dose adjustment required for raltegravir.
ANTIBIOTICS		
Clarithromycin 500 mg twice daily (atazanavir 400 mg once daily)	Clarithromycin AUC: ↑94% (↑75% ↑116%) Clarithromycin C_{max}: ↑50% (↑32% ↑71%) Clarithromycin C_{min}: ↑160% (↑135% ↑188%) 14-OH clarithromycin 14-OH clarithromycin AUC: ↓70% (↓74% ↓66%) 14-OH clarithromycin C_{max}: ↓72% (↓76% ↓67%) 14-OH clarithromycin C_{min}: ↓62% (↓66% ↓58%) Atazanavir AUC: ↑28% (↑16% ↑43%) Atazanavir C_{max}: ↔6% (↓7% ↑20%) Atazanavir C_{min}: ↑91% (↑66% ↑121%) A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.	No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ is co-administered with clarithromycin.
ANTIFUNGALS		
Ketoconazole 200 mg once daily (atazanavir 400 mg once daily)	No significant effect on atazanavir concentrations was observed.	Ketoconazole and itraconazole should be used cautiously with REYATAZ/ritonavir, high doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.
Itraconazole	Itraconazole, like ketoconazole, is a strong inhibitor as well as a substrate of CYP3A4.	
	Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Voriconazole 200 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) Subjects with at least one functional CYP2C19 allele.	Voriconazole AUC: ↓33% (↓42% ↓22%) Voriconazole C_{max}: ↓10% (↓22% ↓4%) Voriconazole C_{min}: ↓39% (↓49% ↓28%) Atazanavir AUC: ↓12% (↓18% ↓5%) Atazanavir C_{max}: ↓13% (↓20% ↓4%) Atazanavir C_{min}: ↓20% (↓28% ↓10%) Ritonavir AUC: ↓12% (↓17% ↓7%) Ritonavir C_{max}: ↓9% (↓17% ↔0%) Ritonavir C_{min}: ↓25% (↓35% ↓14%) In the majority of patients with at least one functional CYP2C19 allele, a reduction in both voriconazole and atazanavir exposures are expected.	Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see section 4.4). At the time voriconazole treatment is required, a patient's CYP2C19 genotype should be performed if feasible. Therefore if the combination is unavoidable, the following recommendations are made according to the CYP2C19 status: - in patients with at least one functional CYP2C19 allele, close clinical monitoring for a loss of both voriconazole (clinical signs) and atazanavir (virologic response) efficacy is recommended. - in patients without a functional CYP2C19 allele, close clinical and laboratory monitoring of voriconazole-associated adverse events is recommended. If genotyping is not feasible, full monitoring of safety and efficacy should be performed.
Voriconazole 50 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) Subjects without a functional CYP2C19 allele.	Voriconazole AUC: ↑561% (↑451% ↑699%) Voriconazole C_{max}: ↑438% (↑355% ↑539%) Voriconazole C_{min}: ↑765% (↑571% ↑1,020%) Atazanavir AUC: ↓20% (↓35% ↓3%) Atazanavir C_{max}: ↓19% (↓34% ↔0.2%) Atazanavir C_{min}: ↓31% (↓46% ↓13%) Ritonavir AUC: ↓11% (↓20% ↓1%) Ritonavir C_{max}: ↓11% (↓24% ↑4%) Ritonavir C_{min}: ↓19% (↓35% ↑1%) In a small number of patients without a functional CYP2C19 allele, significantly increased voriconazole exposures are expected.	
Fluconazole 200 mg once daily (atazanavir 300 mg and ritonavir 100 mg once daily)	Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole.	No dosage adjustments are needed for fluconazole and REYATAZ.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTIMYCOBACTERIAL		
Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg once daily)	Rifabutin AUC: ↑48% (↑19% ↑84%)** Rifabutin C_{max}: ↑149% (↑103% ↑206%)** Rifabutin C_{min}: ↑40% (↑5% ↑87%)** 25-O-desacetyl-rifabutin AUC: ↑990% (↑714% ↑1 361%)** 25-O-desacetyl-rifabutin C_{max}: ↑677% (↑513% ↑883%)** 25-O-desacetyl-rifabutin C_{min}: ↑1 045% (↑715% ↑1 510%)** **When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑119% (↑78% ↑169%). In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.	When given with REYATAZ, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. 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. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ.
Rifampicin	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and REYATAZ is contraindicated (see section 4.3).
ANTIPSYCHOTICS		
Quetiapine	Due to CYP3A4 inhibition by REYATAZ, concentrations of quetiapine are expected to increase.	Co-administration of quetiapine with REYATAZ is contraindicated as REYATAZ may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see section 4.3).
Lurasidone	REYATAZ is expected to increase plasma levels of lurasidone due to CYP3A4 inhibition.	Co-administration of lurasidone with REYATAZ is contraindicated as this may increase lurasidone-related toxicity (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ACID REDUCING AGENTS		
H_2-Receptor antagonists		
Without Tenofovir		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily		**For patients not taking tenofovir,** if REYATAZ 300 mg/ritonavir 100 mg and H_2-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg twice daily should not be exceeded. If a higher dose of an H_2-receptor antagonist is required (e.g., famotidine 40 mg twice daily or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.
Famotidine 20 mg twice daily	Atazanavir AUC: ↓18% (↓25% ↑1%) Atazanavir C_{max}: ↓20% (↓32% ↓7%) Atazanavir C_{min}: ↔1% (↓16% ↑18%)	
Famotidine 40 mg twice daily	Atazanavir AUC: ↓23% (↓32% ↓14%) Atazanavir C_{max}: ↓23% (↓33% ↓12%) Atazanavir C_{min}: ↓20% (↓31% ↓8%)	
In healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg once daily		
Famotidine 40 mg twice daily	Atazanavir AUC: ↔3% (↓14% ↑22%) Atazanavir C_{max}: ↔2% (↓13% ↑8%) Atazanavir C_{min}: ↓14% (↓32% ↑8%)	
With Tenofovir disoproxil fumarate 300 mg once daily (equivalent to 245 mg tenofovir disoproxil)		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg once daily		**For patients who are taking tenofovir disoproxil fumarate,** if REYATAZ/ritonavir with both tenofovir disoproxil fumarate and an H_2-receptor antagonist are co-administered, a dose increase of REYATAZ to 400 mg with 100 mg of ritonavir is recommended. A dose equivalent to famotidine 40 mg twice daily should not be exceeded.
Famotidine 20 mg twice daily	Atazanavir AUC: ↓21% (↓34% ↓4%)* Atazanavir C_{max}: ↓21% (↓36% ↓4%)* Atazanavir C_{min}: ↓19% (↓37% ↑5%)*	
Famotidine 40 mg twice daily	Atazanavir AUC: ↓24% (↓36% ↓11%)* Atazanavir C_{max}: ↓23% (↓36% ↓8%)* Atazanavir C_{min}: ↓25% (↓47% ↑7%)*	
In HIV-infected patients with atazanavir/ritonavir at an increased dose of 400/100 mg once daily		
Famotidine 20 mg twice daily	Atazanavir AUC: ↑18% (↑6.5% ↑30%)* Atazanavir C_{max}: ↑18% (↑6.7% ↑31%)* Atazanavir C_{min}: ↑24% (↑10% ↑39%)*	
Famotidine 40 mg twice daily	Atazanavir AUC: ↔2.3% (↓13% ↑10%)* Atazanavir C_{max}: ↔5% (↓17% ↑8.4%)* Atazanavir C_{min}: ↔1.3% (↓10% ↑15)*	
	*When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg *without tenofovir disoproxil fumarate*, atazanavir concentrations are expected to be additionally decreased by about 20%. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H_2-blockers.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Proton pump inhibitors		
Omeprazole 40 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (am): 2 hr after omeprazole Atazanavir AUC: ↓61% (↓65% ↓55%) Atazanavir C_{max}: ↓66% (↓62% ↓49%) Atazanavir C_{min}: ↓65% (↓71% ↓59%)	Co-administration of REYATAZ with ritonavir and proton pump inhibitors is not recommended. If the combination is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4).
Omeprazole 20 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (am): 1 hr after omeprazole Atazanavir AUC: ↓30% (↓43% ↓14%)* Atazanavir C_{max}: ↓31% (↓42% ↓17%)* Atazanavir C_{min}: ↓31% (↓46% ↓12%)* *When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily. The decrease in AUC, C_{max}, and C_{min} was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.	
Antacids		
Antacids and medicinal products containing buffers	Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ.	REYATAZ should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by REYATAZ and/or ritonavir.	Co-administration of alfuzosin with REYATAZ is contraindicated (see section 4.3)
ANTICOAGULANTS		
Direct-acting oral anticoagulants (DOACs)		
Apixaban **Rivaroxaban**	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.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Dabigatran	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.
Edoxaban	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. Please refer to the edoxaban SmPC sections 4.2 and 4.5 for appropriate edoxaban dosage recommendations for co-administration with P-gp inhibitors.
Vitamin K antagonists		
Warfarin	Co-administration with REYATAZ has the potential to increase or decrease warfarin concentrations.	It is recommended that the International Normalised Ratio (INR) be monitored carefully during treatment with REYATAZ, especially when commencing therapy.
ANTIEPILEPTICS		
Carbamazepine	REYATAZ may increase plasma levels of carbamazepine due to CYP3A4 inhibition. Due to carbamazepine inducing effect, a reduction in REYATAZ exposure cannot be ruled out.	Carbamazepine in combination with REYATAZ (with or without ritonavir) is contraindicated due to the risk for loss of virologic response and development of resistance (see section 4.3). Close monitoring of the patient's virologic response should be exercised.
Phenytoin, phenobarbital	Ritonavir may decrease plasma levels of phenytoin and/or phenobarbital due to CYP2C9 and CYP2C19 induction. Due to phenytoin/phenobarbital inducing effect, a reduction in REYATAZ exposure cannot be ruled out.	Phenobarbital and phenytoin in combination with REYATAZ (with or without ritonavir), are contraindicated, due to the risk for loss of virologic response and development of resistance (see section 4.3) Close monitoring of patient's virologic response should be exercised.
Lamotrigine	Co-administration of lamotrigine and REYATAZ/ritonavir may decrease lamotrigine plasma concentrations due to UGT1A4 induction.	Lamotrigine should be used with caution in combination with REYATAZ/ritonavir. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		
Apalutamide	The mechanism of interaction is CYP3A4 induction by apalutamide and CYP3A4 inhibition by atazanavir/ritonavir.	Co-administration with REYATAZ (with or without ritonavir) is contraindicated due to the potential for decreased atazanavir and ritonavir plasma concentration with subsequent loss of virologic response and possible resistance to the class of protease inhibitors (see section 4.3). In addition, serum concentrations of apalutamide may be increased when coadministered with atazanavir/ritonavir, resulting in the potential for serious adverse events including seizure.
Encorafenib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of encorafenib with REYATAZ (with or without ritonavir) is contraindicated due to the potential for loss of virologic response, development of resistance, increase in encorafenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation (see section 4.3).
Ivosidenib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of ivosidenib with REYATAZ (with or without ritonavir) is contraindicated due to potential for loss of virologic response, development of resistance, increase in ivosidenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation (see section 4.3).
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If REYATAZ is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.
Immunosuppressants		
Cyclosporin **Tacrolimus** **Sirolimus**	Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ due to CYP3A4 inhibition.	More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Amiodarone, **Systemic lidocaine,** **Quinidine**	Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ.	Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Calcium channel blockers		
Bepridil	REYATAZ should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil is contraindicated (see section 4.3)
Diltiazem 180 mg once daily (atazanavir 400 mg once daily)	Diltiazem AUC: ↑125% (↑109% ↑141%) Diltiazem C_{max}: ↑98% (↑78% ↑119%) Diltiazem C_{min}: ↑142% (↑114% ↑173%) Desacetyl-diltiazem AUC: ↑165% (↑145% ↑187%) Desacetyl-diltiazem C_{max}: ↑172% (↑144% ↑203%) Desacetyl-diltiazem C_{min}: ↑121% (↑102% ↑142%) No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.	An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.
Verapamil	Serum concentrations of verapamil may be increased by REYATAZ due to CYP3A4 inhibition.	Caution should be exercised when verapamil is co-administered with REYATAZ.
CORTICOSTEROIDS		
Dexamethasone and other corticosteroids (all routes of administration)	Co-administration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of REYATAZ and development of resistance to atazanavir and/or ritonavir. Alternative corticosteroids should be considered. The mechanism of interaction is CYP3A4 induction by dexamethasone and CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration with corticosteroids (all routes of administration) that are metabolised by CYP3A, particularly for long-term use, may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. The potential benefit of treatment versus the risk of systemic corticosteroid effects should be considered. For co-administration of cutaneously administered corticosteroids sensitive to CYP3A inhibition, consult the Summary of Product Characteristics of the corticosteroid for condition or uses that augment its systemic absorption.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules twice daily) And **Inhaled/Nasal Corticosteroids**	The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82%-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition. Concomitant use of REYATAZ (with or without ritonavir) and other Inhaled/Nasal Corticosteroids is expected to produce the same effects.	Co-administration of REYATAZ/ritonavir and these glucocorticoids metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period. Concomitant use of Inhaled/Nasal Corticosteroids and REYATAZ (with or without ritonavir) may increase plasma concentrations of Inhaled/Nasal corticosteroids. Use with caution. Consider alternatives to Inhaled/Nasal Corticosteroids, particularly for long-term use.
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		
Sildenafil, tadalafil, vardenafil	Sildenafil, tadalafil, and vardenafil are metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of this interaction is CYP3A4 inhibition.	Patients should be warned about these possible side effects when using PDE5 inhibitors for erectile dysfunction with REYATAZ (see section 4.4). Also see PULMONARY ARTERIAL HYPERTENSION in this table for further information regarding co-administration of REYATAZ with sildenafil.
GONADOTROPIN-RELEASING HORMONE (GnRH) RECEPTOR ANTAGONISTS		
Elagolix	The mechanism of interaction is anticipated increase in elagolix exposure in the presence of CYP3A4 inhibition by atazanavir and/or ritonavir.	Concomitant use of elagolix 200 mg twice daily with REYATAZ (with or without ritonavir) for more than 1 month is not recommended due to the potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily with REYATAZ (with or without ritonavir) to 6 months.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
KINASE INHIBITORS		
Fostamatinib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Concomitant use of fostamatinib with REYATAZ (with or without ritonavir) may increase the plasma concentration of R406, the active metabolite of fostamatinib. Monitor for toxicities of R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
HERBAL PRODUCTS		
St. John's wort (Hypericum perforatum)	Concomitant use of St. John's wort with REYATAZ may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3).	Co-administration of REYATAZ with products containing St. John's wort is contraindicated.
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol 25 µg + norgestimate (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Ethinyloestradiol AUC: ↓19% (↓25% ↓13%) Ethinyloestradiol C_{max}: ↓16% (↓26% ↓5%) Ethinyloestradiol C_{min}: ↓37% (↓45% ↓29%) Norgestimate AUC: ↑85% (↑67% ↑105%) Norgestimate C_{max}: ↑68% (↑51% ↑88%) Norgestimate C_{min}: ↑102% (↑77% ↑131%) While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side-effects (e.g., insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Ethinyloestradiol 35 µg + norethindrone (atazanavir 400 mg once daily)	Ethinyloestradiol AUC: ↑48% (↑31% ↑68%) Ethinyloestradiol C_{max}: ↑15% (↓1% ↑32%) Ethinyloestradiol C_{min}: ↑91% (↑57% ↑133%) Norethindrone AUC: ↑110% (↑68% ↑162%) Norethindrone C_{max}: ↑67% (↑42% ↑196%) Norethindrone C_{min}: ↑262% (↑157% ↑409%) The increase in progestin exposure may lead to related side effects (e.g., insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	
LIPID-MODIFYING AGENTS		
HMG-CoA reductase inhibitors		
Simvastatin **Lovastatin**	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ may result in increased concentrations.	Co-administration of simvastatin or lovastatin with REYATAZ is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see section 4.3).
Atorvastatin	The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.	Co-administration of atorvastatin with REYATAZ is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring (see section 4.4).
Pravastatin **Fluvastatin**	Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9.	Caution should be exercised.
Other lipid-modifying agents		
Lomitapide	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 (see section 4.3).
INHALED BETA AGONISTS		
Salmeterol	Co-administration with REYATAZ may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of salmeterol with REYATAZ is not recommended (see section 4.4).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
OPIOIDS		
Buprenorphine, once daily, stable maintenance dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Buprenorphine AUC: ↑67% Buprenorphine C_{max}: ↑37% Buprenorphine C_{min}: ↑69% Norbuprenorphine AUC: ↑105% Norbuprenorphine C_{max}: ↑61% Norbuprenorphine C_{min}: ↑101% The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir (when given with ritonavir) were not significantly affected.	Co-administration with REYATAZ with ritonavir warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Methadone, stable maintenance dose (atazanavir 400 mg once daily)	No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ, based on these data.	No dosage adjustment is necessary if methadone is co-administered with REYATAZ.
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		
Sildenafil	Co-administration with REYATAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-inhibitor-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	A safe and effective dose in combination with REYATAZ has not been established for sildenafil when used to treat pulmonary arterial hypertension. Sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated (see section 4.3).
SEDATIVES		
Benzodiazepines		
Midazolam **Triazolam**	Midazolam and triazolam are extensively metabolised by CYP3A4. Co-administration with REYATAZ may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4-fold increase in midazolam plasma levels.	Co-administration of REYATAZ with triazolam or orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co-administration of REYATAZ and parenteral midazolam. If REYATAZ is co-administered with parenteral 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.

In case of withdrawal of ritonavir from the recommended atazanavir-boosted regimen (see section 4.4)
The same recommendations for drug interactions would apply except:

- that co-administration is not recommended with tenofovir, proton pump inhibitors, and buprenorphine and contraindicated with carbamazepine, phenytoin and phenobarbital.
- 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.
- the need to consider that:
  - co-administration of apixaban, dabigatran, or rivaroxaban and REYATAZ without ritonavir may affect apixaban, dabigatran, or rivaroxaban concentrations
  - 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
  - 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
  - no dose adjustment of lamotrigine is required

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data in pregnant women (between 300-1 000 pregnancy outcomes) indicate no malformative toxicity of atazanavir. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of REYATAZ with ritonavir may be considered during pregnancy only if the potential benefit justifies the potential risk.

In clinical trial AI424-182 REYATAZ/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 pregnant women during the second or third trimester. Six of 20 (30%) women on REYATAZ/ritonavir 300/100 mg and 13 of 21 (62%) women on REYATAZ/ritonavir 400/100 mg experienced grades 3 to 4 hyperbilirubinaemia. There were no cases of lactic acidosis observed in the clinical trial AI424-182.

The study assessed 40 infants who received antiretroviral prophylactic treatment (which did not include REYATAZ) and were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. Three of 20 infants (15%) born to women treated with REYATAZ/ritonavir 300/100 mg and four of 20 infants (20%) born to women treated with REYATAZ/ritonavir 400/100 mg experienced grade 3-4 bilirubin. There was no evidence of pathologic jaundice and six of 40 infants in this study received phototherapy for a maximum of 4 days. There were no reported cases of kernicterus in neonates.

For dosing recommendations see section 4.2 and for pharmacokinetic data see section 5.2.

It is not known whether REYATAZ with ritonavir administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring should be considered.

Breast-feeding

Atazanavir has been detected in human milk. In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

In a nonclinical fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown 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 (see section 4.4).

Tabulated list of adverse reactions

Assessment of adverse reactions for REYATAZ is based on safety data from clinical studies and post-marketing experience. Frequency is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:	uncommon: hypersensitivity
Metabolism and nutrition disorders:	uncommon: weight decreased, weight gain, anorexia, appetite increased
Psychiatric disorders:	uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream
Nervous system disorders:	common: headache; uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia
Eye disorders:	common: ocular icterus
Cardiac disorders:	uncommon: torsades de pointes[a] rare: QTc prolongation[a], oedema, palpitation

Vascular disorders:	uncommon: hypertension
Respiratory, thoracic and mediastinal disorders:	uncommon: dyspnoea
Gastrointestinal disorders:	common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia; uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth
Hepatobiliary disorders:	common: jaundice; uncommon: hepatitis, cholelithiasis[a], cholestasis[a]; rare: hepatosplenomegaly, cholecystitis[a]
Skin and subcutaneous tissue disorders:	common: rash; uncommon: erythema multiforme[a,b], toxic skin eruptions[a,b], drug rash with eosinophilia and systemic symptoms (DRESS) syndrome[a,b], angioedema[a], urticaria, alopecia, pruritus; rare: Stevens-Johnson syndrome[a,b], vesiculobullous rash, eczema, vasodilatation
Musculoskeletal and connective tissue disorders:	uncommon: muscle atrophy, arthralgia, myalgia; rare: myopathy
Renal and urinary disorders:	uncommon: nephrolithiasis, haematuria, proteinuria, pollakiuria, interstitial nephritis, chronic kidney disease[a]; rare: kidney pain
Reproductive system and breast disorders:	uncommon: gynaecomastia
General disorders and administration site conditions:	common: fatigue; uncommon: chest pain, malaise, pyrexia, asthenia; rare: gait disturbance

[a] These adverse reactions were identified through post-marketing surveillance, however, the frequencies were estimated from a statistical calculation based on the total number of patients exposed to REYATAZ in randomised controlled and other available clinical trials (n = 2 321).
[b] See description of selected adverse reactions for more details.

Description of selected adverse reactions

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Rash and associated syndromes
Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with the use of REYATAZ (see section 4.4).

Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated

indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naïve patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

Paediatric population

In a clinical study AI424-020, paediatric patients 3 months to less than 18 years of age who received either the oral powder or capsule formulation had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in this study was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

In clinical studies AI424-397 and AI424-451, paediatric patients 3 months to less than 11 years of age had a mean duration of treatment with REYATAZ oral powder of 80 weeks. No deaths were reported. The safety profile in these studies was overall comparable to that seen in previous paediatric and adult studies. The most frequently reported laboratory abnormalities in paediatric patients receiving REYATAZ oral powder was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4; 16%) and increased amylase (Grade 3-4; 33%), generally of non-pancreatic origin. Elevation in ALT levels were more frequently reported in paediatric patients in these studies than in adults.

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to

high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE08

Mechanism of action

Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Resistance

Antiretroviral treatment naïve adult patients
In clinical trials of antiretroviral treatment-naïve patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment-naïve patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 3: De novo substitutions in treatment-naïve patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

Frequency	de novo PI substitution (n = 26)[a]
> 20%	none
10-20%	none

[a] Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/mL).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients
In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naïve patients.

Table 4: De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

Frequency	de novo PI substitution (n = 35)[a,b]
> 20%	M36, M46, I54, A71, V82
10-20%	L10, I15, K20, V32, E35, S37, F53, I62, G73, I84, L90

[a] Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/mL).
[b] Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]> 5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA)

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

Clinical results

In antiretroviral naïve adult patients
Study 138 is an international randomised, open-label, multicenter, prospective trial of treatment-naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed-dose tenofovir disoproxil fumarate/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/mL at Week 48 (Table 5).

Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).

Table 5: Efficacy Outcomes in Study 138[a]

Parameter	REYATAZ/ritonavir[b] (300 mg/100 mg once daily) n = 440		Lopinavir/ritonavir[c] (400 mg/100 mg twice daily) n = 443	
	Week 48	Week 96	Week 48	Week 96
HIV RNA < 50 copies/mL, %				
All patients[d]	78	74	76	68
Difference estimate [95% CI][d]	Week 48: 1.7% [-3.8%, 7.1%] Week 96: 6.1% [0.3%, 12.0%]			
Per protocol analysis[e]	86 (n = 392[f])	91 (n = 352)	89 (n = 372)	89 (n = 331)
Difference estimate[e] [95% CI]	Week 48: -3% [-7.6%, 1.5%] Week 96: 2.2% [-2.3%, 6.7%]			
HIV RNA < 50 copies/mL, % by Baseline Characteristic[d]				
HIV RNA < 100,000 copies/mL	82 (n = 217)	75 (n = 217)	81 (n = 218)	70 (n = 218)
≥ 100,000 copies/mL	74 (n = 223)	74 (n = 223)	72 (n = 225)	66 (n = 225)
CD4 count < 50 cells/mm^3	78 (n = 58)	78 (n = 58)	63 (n = 48)	58 (n = 48)
50 to < 100 cells/mm^3	76 (n = 45)	71 (n = 45)	69 (n = 29)	69 (n = 29)
100 to < 200 cells/mm^3	75 (n = 106)	71 (n = 106)	78 (n = 134)	70 (n = 134)
≥ 200 cells/mm^3	80 (n = 222)	76 (n = 222)	80 (n = 228)	69 (n = 228)

Parameter	REYATAZ/ritonavir[b] (300 mg/100 mg once daily) n = 440		Lopinavir/ritonavir[c] (400 mg/100 mg twice daily) n = 443	
HIV RNA Mean Change from Baseline, log_{10} copies/mL				
All patients	-3.09 (n = 397)	-3.21 (n = 360)	-3.13 (n = 379)	-3.19 (n = 340)
CD4 Mean Change from Baseline, cells/mm^3				
All patients	203 (n = 370)	268 (n = 336)	219 (n = 363)	290 (n = 317)
CD4 Mean Change from Baseline, cells/mm^3 by Baseline Characteristic				
HIV RNA < 100,000 copies/mL	179 (n = 183)	243 (n = 163)	194 (n = 183)	267 (n = 152)
≥ 100,000 copies/mL	227 (n = 187)	291 (n = 173)	245 (n = 180)	310 (n = 165)

[a] Mean baseline CD4 cell count was 214 cells/mm^3 (range 2 to 810 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.94 log_{10} copies/mL (range 2.6 to 5.88 log_{10} copies/mL)
[b] REYATAZ/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[c] Lopinavir/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[d] Intent-to-treat analysis, with missing values considered as failures.
[e] Per protocol analysis: Excluding non-completers and patients with major protocol deviations.
[f] Number of patients evaluable.

Data on withdrawal of ritonavir from atazanavir boosted regimen (see also section 4.4)

Study 136 (INDUMA)
In an open-label, randomised, comparative study following a 26- to 30-week induction phase with REYATAZ 300 mg + ritonavir 100 mg once daily and two NRTIs, unboosted REYATAZ 400 mg once daily and two NRTIs administered during a 48-week maintenance phase (n = 87) had similar antiviral efficacy compared with REYATAZ + ritonavir and two NRTIs (n = 85) in HIV-infected subjects with fully suppressed HIV replication, as assessed by the proportion of subjects with HIV RNA < 50 copies/mL: 78% of subjects on unboosted REYATAZ and two NRTIs compared with 75% on REYATAZ + ritonavir and two NRTIs.

Eleven subjects (13%) in the unboosted REYATAZ group and 6 (7%) in the REYATAZ + ritonavir group, had virologic rebound. Four subjects in the unboosted REYATAZ group and 2 in the REYATAZ + ritonavir group had HIV RNA > 500 copies/mL during the maintenance phase. No subject in either group showed emergence of protease inhibitor resistance. The M184V substitution in reverse transcriptase, which confers resistance to lamivudine and emtricitabine, was detected in 2 subjects in the unboosted REYATAZ and 1 subject in the REYATAZ + ritonavir group.

There were fewer treatment discontinuations in the unboosted REYATAZ group (1 vs. 4 subjects in the REYATAZ + ritonavir group). There was less hyperbilirubinaemia and jaundice in the unboosted REYATAZ group compared with the REYATAZ + ritonavir group (18 and 28 subjects, respectively).

In antiretroviral experienced adult patients
Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed-dose combination twice daily), each in combination with tenofovir disoproxil fumarate (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).

Table 6: Efficacy Outcomes at Week 48[a] and at Week 96 (Study 045)

Parameter	ATV/RTV[b] (300 mg/100 mg once daily) n = 120		LPV/RTV[c] (400 mg/100 mg twice daily) n = 123		Time-averaged difference ATV/RTV-LPV/RTV [97.5% CI[d]]	
	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
HIV RNA Mean Change from Baseline, log_{10} copies/mL						
All patients	-1.93 (n = 90[e])	-2.29 (n = 64)	-1.87 (n = 99)	-2.08 (n = 65)	0.13 [-0.12, 0.39]	0.14 [-0.13, 0.41]
HIV RNA < 50 copies/mL, %[f] (responder/evaluable)						
All patients	36 (43/120)	32 (38/120)	42 (52/123)	35 (41/118)	NA	NA
HIV RNA < 50 copies/mL by select baseline PI substitutions,[f, g] % (responder/evaluable)						
0-2	44 (28/63)	41 (26/63)	56 (32/57)	48 (26/54)	NA	NA
3	18 (2/11)	9 (1/11)	38 (6/16)	33 (5/15)	NA	NA
≥ 4	27 (12/45)	24 (11/45)	28 (14/50)	20 (10/49)	NA	NA
CD4 Mean Change from Baseline, cells/mm^3						
All patients	110 (n = 83)	122 (n = 60)	121 (n = 94)	154 (n = 60)	NA	NA

[a] The mean baseline CD4 cell count was 337 cells/mm^3 (range: 14 to 1,543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/mL (range: 2.6 to 5.88 log_{10} copies/mL).
[b] ATV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[c] LPV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[d] Confidence interval.
[e] Number of patients evaluable.
[f] Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/mL were 53% and 43% for ATV/RTV and 54% and 46% for LPV/RTV at Weeks 48 and 96 respectively.
[g] Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.
NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/mL (< 50 copies/mL) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/mL (< 50 copies/mL) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48% of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

Paediatric population
Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial AI424-020 conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naïve and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naïve paediatric patients, the mean baseline CD4 cell count was 344 cells/mm^3 (range: 2 to 800 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.67 log_{10} copies/mL (range: 3.70 to 5.00 log_{10} copies/mL). For treatment-experienced paediatric patients, the mean baseline CD4 cell count was 522 cells/mm^3 (range: 100 to 1157 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.09 log_{10} copies/mL (range: 3.28 to 5.00 log_{10} copies/mL).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week 48 (Study AI424-020)

Parameter	Treatment-Naïve REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n = 16	Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n = 25
HIV RNA < 50 copies/mL, %[a]		
All patients	81 (13/16)	24 (6/25)
HIV RNA < 400 copies/mL, %[a]		
All patients	88 (14/16)	32 (8/25)
CD4 Mean Change from Baseline, cells/mm^3		
All patients	293 (n = 14[b])	229 (n = 14[b])
HIV RNA < 50 copies/mL by select baseline PI substitutions,[c] % (responder/evaluable[d])		
0-2	NA	27 (4/15)
3	NA	-
≥ 4	NA	0 (0/3)

[a] Intent-to-treat analysis, with missing values considered as failures.
[b] Number of patients evaluable.
[c] PI major L24I, D30N, V32I, L33F, M46IL, I47AV, G48V, I50LV, F53LY,I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M; PI minor: L10CFIRV, V11I, E35G, K43T, Q58E, A71ILTV, G73ACST, T74P, N83D, L89V.
[d] Includes patients with baseline resistance data.
NA = not applicable.

5.2 Pharmacokinetic properties

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition.

Absorption: in HIV-infected patients (n = 33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/mL, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/mL and 44185 (51%) ng•h/mL, respectively.

In HIV-infected patients (n = 13), multiple dosing of REYATAZ 400 mg (without ritonavir) once daily with food produced a geometric mean (CV%) for atazanavir C_{max} of 2298 (71) ng/mL, with time to C_{max} of approximately 2.0 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC were 120 (109) ng/mL and 14874 (91) ng•h/mL, respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24 hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately

33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

Distribution: atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/mL. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/mL). In a multiple-dose study in HIV-infected patients dosed with 400-mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

Metabolism: studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

Elimination: following a single 400 mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n = 33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

Special populations

Renal impairment: in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n = 20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)

Hepatic impairment: atazanavir is metabolised and eliminated primarily by the liver. REYATAZ (without ritonavir) has been studied in adult subjects with moderate-to-severe hepatic impairment (14 Child-Pugh Class B and 2 Child-Pugh Class C subjects) after a single 400-mg dose. The mean $AUC_{(0-\infty)}$ was 42% greater in subjects with impaired hepatic function than in healthy subjects. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy subjects. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

Age/Gender: a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

Race: a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.

Pregnancy:
The pharmacokinetic data from HIV-infected pregnant women receiving REYATAZ capsules with ritonavir are presented in Table 8.

Table 8: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

	atazanavir 300 mg with ritonavir 100 mg		
Pharmacokinetic Parameter	**2nd Trimester** (n = 9)	**3rd Trimester** (n = 20)	**postpartum**[a] (n = 36)
C_{max} ng/mL Geometric mean (CV%)	3 729.09 (39)	3 291.46 (48)	5 649.10 (31)
AUC ng•h/mL Geometric mean (CV%)	34 399.1 (37)	34 251.5 (43)	60 532.7 (33)
C_{min} ng/mL[b] Geometric mean (CV%)	663.78 (36)	668.48 (50)	1 420.64 (47)

[a] Atazanavir peak concentrations and AUCs were found to be approximately 26-40% higher during the postpartum period (4-12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2-fold higher during the postpartum period when compared to those observed historically in HIV-infected non-pregnant patients.
[b] C_{min} is concentration 24 hours post-dose.

Paediatric population
There is a trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed, however at recommended doses, geometric mean atazanavir exposures (C_{min}, C_{max}, and AUC) in paediatric patients are expected to be similar to those observed in adults.

5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During *in vitro* studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at C_{max} in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD_{90}) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic activation. In *in vivo* studies in rats, atazanavir

did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic *in vitro*.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an *in vitro* ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

REYATAZ 200 mg hard capsules

Capsule contents: crospovidone, lactose monohydrate, and magnesium stearate

Capsule shells: gelatin, indigocarmin (E132), and titanium dioxide (E171)

White ink containing: shellac, titanium dioxide (E171), ammonium hydroxide, propylene glycol, and simethicone

REYATAZ 300 mg hard capsules

Capsule contents: crospovidone, lactose monohydrate, and magnesium stearate

Capsule shells: gelatin, red iron oxide, black iron oxide, yellow iron oxide, indigocarmin (E132), and titanium dioxide (E171)

White ink containing: shellac, titanium dioxide (E171), ammonium hydroxide, propylene glycol, and simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

REYATAZ 200 mg hard capsules

Each carton contains one high-density polyethylene (HDPE) bottle or three high-density polyethylene (HDPE) bottles closed with child-resistant polypropylene closure. Each bottle contains 60 hard capsules.

Each carton contains 60 x 1 capsules; 10 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

REYATAZ 300 mg hard capsules

Each carton contains one high-density polyethylene (HDPE) bottle or three high-density polyethylene (HDPE) bottles closed with child-resistant polypropylene closure. Each bottle contains 30 hard capsules.

Each carton contains 30 x 1 capsules; 5 blister cards of 6 x 1 capsules each in Alu/Alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/005-006; 008-011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 06 February 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 50 mg oral powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of 1.5 g oral powder contains 50 mg of atazanavir (as sulphate).

Excipient with known effect: 63 mg of aspartame; 1 305.15 mg of sucrose per sachet (1.5 g oral powder).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder
Off-white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REYATAZ oral powder, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected paediatric patients at least 3 months of age and weighing at least 5 kg (see section 4.2).

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Paediatric patients (at least 3 months of age and weighing at least 5 kg)
The doses of atazanavir oral powder and ritonavir for paediatric patients are based on body weight as shown in Table 1. REYATAZ oral powder must be taken with ritonavir and has to be taken with food.

Table 1: Dose of REYATAZ oral powder with ritonavir for paediatric patients[a] (at least 3 months of age and weighing at least 5 kg)

Body weight (kg)	REYATAZ once daily dose	ritonavir once daily dose
at least 5 to less than 15	200 mg (4 sachets[b])	80 mg[c]
at least 15 to less than 35	250 mg (5 sachets[b])	80 mg[c]
at least 35	300 mg (6 sachets[b])	100 mg[d]

[a] The same recommendations regarding the timing and maximum doses of concomitant proton pump inhibitors and H_2-receptor antagonists in adults also apply to paediatric patients (see section 4.5).
[b] Each sachet contains 50 mg of atazanavir.
[c] Ritonavir oral solution.
[d] Ritonavir oral solution or capsule/tablet.

REYATAZ capsules are available for paediatric patients at least 6 years of age who weigh at least 15 kg and who are able to swallow capsules (see Summary of Product Characteristics for REYATAZ capsules). Switching from REYATAZ oral powder to REYATAZ capsules is encouraged as soon as patients are able to consistently swallow capsules.

When transitioning between formulations, a change in dose may be needed. Consult the dosing table for the specific formulation (see Summary of Product Characteristics for REYATAZ capsules).

Special populations

Renal impairment
No dosage adjustment is needed. REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

Hepatic impairment
REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

Pregnancy and Postpartum
During the second and third trimesters of pregnancy:
REYATAZ 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir 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 (TDM) may be considered to ensure adequate exposure.

The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to reduce its exposure (e.g., tenofovir disoproxil or H_2-receptor antagonists).

- If tenofovir disoproxil or an H_2-receptor antagonist is needed, a dose increase to REYATAZ 400 mg with ritonavir 100 mg with TDM may be considered (see sections 4.6 and 5.2).
- It is not recommended to use REYATAZ with ritonavir for pregnant patients who are receiving both tenofovir disoproxil and an H_2-receptor antagonist.

During postpartum:
Following a possible decrease in atazanavir exposure during the second and third trimester, atazanavir exposures might increase during the first two months after delivery (see section 5.2). Therefore, postpartum patients should be closely monitored for adverse reactions.

- During this time, postpartum patients should follow the same dose recommendation as for non-pregnant patients, including those for co-administration of medicinal products known to affect atazanavir exposure (see section 4.5).

Paediatric patients (less than 3 months of age)
REYATAZ has not been studied in children less than 3 months of age and is not recommended because of the potential risk of kernicterus.

Method of administration

For oral use.

REYATAZ oral powder should be taken/given with food (e.g., applesauce or yogurt) or drinks (e.g., milk, infant formula, or water) for infants who can drink from a cup. For young infants (less than 6 months) who cannot eat solid food or drink from a cup, REYATAZ oral powder should be mixed with infant formula and given using an oral syringe, which can be obtained from a pharmacist. Administration of REYATAZ and infant formula using an infant bottle is not recommended because the full dose may not be delivered.

For details on preparation and administration of the REYATAZ oral powder and Instructions for Use, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with moderate to severe hepatic insufficiency (see sections 4.2 and 4.4).

Co-administration with simvastatin or lovastatin (see section 4.5).

Co-administration of the PDE5 inhibitor sildenafil when used for the treatment of pulmonary arterial hypertension (PAH) only (see section 4.5). For co-administration of sildenafil for the treatment of erectile dysfunction see sections 4.4 and 4.5.

Co-administration with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g., quetiapine, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, lurasidone, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5), lomitapide and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).

Co-administration with medicinal products that are strong inducers of CYP3A4 due to the potential for loss of therapeutic effect and development of possible resistance (e.g., rifampicin, St. John's wort, apalutamide, encorafenib, ivosidenib, carbamazepine, phenobarbital and phenytoin) (see section 4.5).

Co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination (see section 4.5).

Co-administration with glecaprevir/pibrentasvir fixed-dose combination (see section 4.5).

4.4 Special warnings and precautions for use

Co-administration of REYATAZ with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted (see Interaction with other Medicinal Products below).

<u>Patients with coexisting conditions</u>

Hepatic impairment
Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal impairment
No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

QT prolongation
Dose-related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). Particular caution should be used when prescribing REYATAZ in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).

Haemophiliac patients
There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to the disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, REYATAZ with ritonavir has been shown to induce dyslipidaemia to a lesser extent than lopinavir with ritonavir in either treatment-naïve patients (Study 138) or treatment-experienced patients (Study 045), (see section 5.1).

Hyperbilirubinaemia

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be evaluated for alternative aetiologies. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT. Combinations of REYATAZ and indinavir have not been studied and co-administration of these medicinal products is not recommended (see section 4.5).

Cholelithiasis

Cholelithiasis has been reported in patients receiving REYATAZ (see section 4.8). Some patients required hospitalisation for additional management and some had complications. If signs or symptoms of cholelithiasis occur, temporary interruption or discontinuation of treatment may be considered.

Chronic kidney disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown

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 (see section 4.8).

Nephrolithiasis

Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). Some patients required hospitalisation for additional management and some had complications. In some cases, nephrolithiasis has been associated with acute renal failure or renal insufficiency. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered.

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Rash and associated syndromes

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in patients receiving REYATAZ. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. REYATAZ should be discontinued if severe rash develops.

The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of REYATAZ, REYATAZ may not be restarted.

Interactions with other medicinal products

The combination of REYATAZ with atorvastatin is not recommended (see section 4.5).

Co-administration of REYATAZ with nevirapine or efavirenz is not recommended (see section 4.5). If the co-administration of REYATAZ with an NNRTI is required, an increase in the dose of both REYATAZ and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.

Atazanavir is metabolised principally by CYP3A4. Co-administration of REYATAZ with ritonavir and medicinal products that induce CYP3A4 is not recommended (see section 4.5).

PDE5-inhibitors used for the treatment of erectile dysfunction: particular caution should be used when prescribing PDE5 inhibitors (sildenafil, tadalafil, or vardenafil) for the treatment of erectile dysfunction in patients receiving REYATAZ with concomitant low-dose ritonavir. Co-administration of REYATAZ with these medicinal products is expected to substantially increase their concentrations and may result in PDE5-associated adverse reactions such as hypotension, visual changes, and priapism (see section 4.5).

Co-administration of voriconazole and REYATAZ with ritonavir is not recommended, unless an assessment of the benefit/risk justifies the use of voriconazole.

In the majority of patients, a reduction in both voriconazole and atazanavir exposures are expected. In a small number of patients without a functional CYP2C19 allele, significantly increased voriconazole exposures are expected (see section 4.5).

Concomitant use of REYATAZ/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Concomitant use of salmeterol and REYATAZ/ritonavir may result in increased cardiovascular adverse events associated with salmeterol. Co-administration of salmeterol and REYATAZ is not recommended (see section 4.5).

The absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause.

Co-administration of REYATAZ with proton pump inhibitors is not recommended (see section 4.5). If the combination of REYATAZ with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided (see section 4.5).

Paediatric population

Safety
Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

Efficacy
Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance.

Excipients

Phenylketonuria
REYATAZ oral powder contains aspartame as a sweetening agent. Aspartame provides a source of phenylalanine and, therefore, may not be suitable for persons with phenylketonuria.

Diabetic population
REYATAZ oral powder contains 1 305.15 mg of sucrose per sachet. For the recommended paediatric dosage, REYATAZ oral powder contains 3 915.45 mg sucrose per 150 mg atazanavir, 5 220.60 mg sucrose per 200 mg atazanavir, 6 525.75 mg sucrose per 250 mg atazanavir, and 7 830.90 mg sucrose per 300 mg atazanavir. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption, or sucrase isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When REYATAZ and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. The Summary of Product Characteristics for ritonavir must be consulted before initiation of therapy with REYATAZ and ritonavir.

Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, REYATAZ with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, lomitapide, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3). Co-administration of REYATAZ with grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination is contraindicated because of the increase in grazoprevir and elbasvir plasma concentrations and potential for the increase in risk of ALT elevations associated with increased grazoprevir concentrations (see section 4.3). Co-administration of REYATAZ with glecaprevir/pibrentasvir fixed-dose combination is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecapreir and pibrentasvir plasma concentrations (see section 4.3).

Other interactions
Interactions between atazanavir/ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors, and other non-antiretroviral medicinal products are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔"). If available, 90% confidence intervals (CI) are shown in parentheses. The studies presented in Table 2 were conducted in healthy subjects unless otherwise noted. Of importance, many studies were conducted with unboosted atazanavir, which is not the approved regimen of atazanavir.

Interactions between atazanavir and other medicinal products, including those for which co-administration is contraindicated, are listed in the table below:

Table 2: Interactions between REYATAZ and other medicinal products

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
ANTI-HCV AGENTS		
Grazoprevir 200 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily)	Atazanavir AUC: ↑43% (↑30% ↑57%) Atazanavir C_{max}: ↑12% (↑1% ↑24%) Atazanavir C_{min}: ↑23% (↑13% ↑134%) Grazoprevir AUC: ↑958% (↑678% ↑1 339%) Grazoprevir C_{max}: ↑524% (↑342% ↑781%) Grazoprevir C_{min}: ↑1 064% (↑696% ↑1 602%) Grazoprevir concentrations were greatly increased when co-administered with atazanavir/ritonavir.	Co-administration of REYATAZ and elbasvir/grazoprevir is contraindicated because of a significant increase in grazoprevir plasma concentrations and an associated potential increase in the risk of ALT elevations (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Elbasvir 50 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily)	Atazanavir AUC: ↑7% (↓2% ↑17%) Atazanavir C_{max}: ↑2% (↓4% ↑8%) Atazanavir C_{min}: ↑15% (↑2% ↑29%) Elbasvir AUC: ↑376% (↑307% ↑456%) Elbasvir C_{max}: ↑315% (↑246% ↑397%) Elbasvir C_{min}: ↑545% (↑451% ↑654%) Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir.	
Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg single dose* (atazanavir 300 mg/ritonavir 100 mg once daily)	Sofosbuvir AUC: ↑40% (↑25% ↑57%) Sofosbuvir C_{max}: ↑29% (↑9% ↑52%) Velpatasvir AUC: ↑93% (↑58% ↑136%) Velpatasvir C_{max}: ↑29% (↑7% ↑56%) Voxilaprevir AUC: ↑331% (↑276% ↑393%) Voxilaprevir C_{max}: ↑342% (↑265% ↑435%) *Lack of pharmacokinetics interaction bounds 70-143% Effect on atazanavir and ritonavir exposure has not been studied. Expected: ↔ Atazanavir ↔ Ritonavir The mechanism of interaction between REYATAZ/ritonavir and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, P-gp, and CYP3A.	Co-administration of REYATAZ with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Co-administration of REYATAZ with voxilaprevir-containing regimens is not recommended.
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (atazanavir 300 mg/ritonavir 100 mg once daily*)	Glecaprevir AUC: ↑553% (↑424% ↑714%) Glecaprevir C_{max}: ↑306% (↑215% ↑423%) Glecaprevir $C_{min:}$ ↑1 330% (↑885% ↑1 970%) Pibrentasvir AUC: ↑64% (↑48% ↑82%) Pibrentasvir $C_{max:}$ ↑29% (↑15% ↑45%) Pibrentasvir C_{min}: ↑129% (↑95% ↑168%) *Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.	Co-administration of REYATAZ with glecaprevir/pibrentasvir is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3)
ANTIPLATELETS		
Ticagrelor	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of REYATAZ with ticagrelor is not recommended due to potential increase in the antiplatelet activity of ticagrelor.
Clopidogrel	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and or/ritonavir.	Co-administration with clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Prasugrel	The mechanism of the interaction is CYP3A4 inhibition by atazanavir and or/ritonavir.	No dose adjustment is needed when prasugrel is co-administered with REYATAZ (with or without ritonavir).
ANTI-RETROVIRALS		
Protease inhibitors: The co-administration of REYATAZ/ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co-administration is not recommended.		
Ritonavir 100 mg once daily (atazanavir 300 mg once daily) Studies conducted in HIV-infected patients.	Atazanavir AUC: ↑250% (↑144% ↑403%)* Atazanavir C_{max}: ↑120% (↑56% ↑211%)* Atazanavir C_{min}: ↑713% (↑359% ↑1 339%)* *In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n = 33) was compared to atazanavir 400 mg without ritonavir (n = 28). The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition.	Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Co-administration of REYATAZ/ritonavir and indinavir is not recommended (see section 4.4).
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine 150 mg twice daily + zidovudine 300 mg twice daily (atazanavir 400 mg once daily)	No significant effect on lamivudine and zidovudine concentrations was observed.	Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of these medicinal products and REYATAZ is not expected to significantly alter the exposure of the co-administered medicinal products.
Abacavir	The co-administration of abacavir and REYATAZ is not expected to significantly alter the exposure of abacavir.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)	Atazanavir, simultaneous administration with ddI+d4T (fasted) Atazanavir AUC: ↓87% (↓92% ↓79%) Atazanavir C_{max}: ↓89% (↓94% ↓82%) Atazanavir C_{min}: ↓84% (↓90% ↓73%) Atazanavir, dosed 1 hr after ddI+d4T (fasted) Atazanavir AUC: ↔3% (↓36% ↑67%) Atazanavir C_{max}: ↑12% (↓33% ↑18%) Atazanavir C_{min}: ↔3% (↓39% ↑73%) Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.	Didanosine should be taken at the fasted state 2 hours after REYATAZ taken with food. The co-administration of stavudine with REYATAZ is not expected to significantly alter the exposure of stavudine.
Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Didanosine (with food) Didanosine AUC: ↓34% (↓41% ↓27%) Didanosine C_{max}: ↓38% (↓48% ↓26%) Didanosine C_{min}: ↑25% (↓8% ↑69%) No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.	
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil. Studies conducted in HIV-infected patients	Atazanavir AUC: ↓22% (↓35% ↓6%)* Atazanavir C_{max}: ↓16% (↓30% ↔0%)* Atazanavir C_{min}: ↓23% (↓43% ↑2%)* *In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir disoproxil fumarate 300 mg (n = 39) was compared to atazanavir/ritonavir 300/100 mg (n = 33). The efficacy of REYATAZ/ritonavir in combination with tenofovir disoproxil fumarate in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir disoproxil fumarate is unknown.	When co-administered with tenofovir disoproxil fumarate, it is recommended that REYATAZ 300 mg be given with ritonavir 100 mg and tenofovir disoproxil fumarate 300 mg (all as a single dose with food).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil.	Tenofovir disoproxil fumarate AUC: ↑37% (↑30% ↑45%) Tenofovir disoproxil fumarate C_{max}: ↑34% (↑20% ↑51%) Tenofovir disoproxil fumarate C_{min}: ↑29% (↑21% ↑36%)	Patients should be closely monitored for tenofovir disoproxil fumarate-associated adverse reactions, including renal disorders.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (pm): all administered with food Atazanavir AUC: ↔0%(↓9% ↑10%)* Atazanavir C_{max}: ↑17%(↑8% ↑27%)* Atazanavir C_{min}: ↓42%(↓51% ↓31%)*	Co-administration of efavirenz and REYATAZ is not recommended (see section 4.4).
Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 200 mg once daily)	Atazanavir (pm): all administered with food Atazanavir AUC: ↔6% (↓10% ↑26%)*/** Atazanavir C_{max}: ↔9% (↓5% ↑26%)*/** Atazanavir C_{min}: ↔12% (↓16% ↑49%)*/** *When compared to REYATAZ 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction. **Based on historical comparison.	
Nevirapine 200 mg twice daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily) Study conducted in HIV-infected patients.	Nevirapine AUC: ↑26% (↑17% ↑36%) Nevirapine C_{max}: ↑21% (↑11% ↑32%) Nevirapine C_{min}: ↑35% (↑25% ↑47%) Atazanavir AUC: ↓19% (↓35% ↑2%)* Atazanavir C_{max}: ↔2% (↓15% ↑24%)* Atazanavir C_{min}: ↓59% (↓73% ↓40%)* *When compared to REYATAZ 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction.	Co-administration of nevirapine and REYATAZ is not recommended (see section 4.4)
Integrase Inhibitors		
Raltegravir 400 mg twice daily (atazanavir/ritonavir)	Raltegravir AUC: ↑41% Raltegravir C_{max}: ↑24% Raltegravir C_{12hr}: ↑77% The mechanism is UGT1A1 inhibition.	No dose adjustment required for raltegravir.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTIBIOTICS		
Clarithromycin 500 mg twice daily (atazanavir 400 mg once daily)	Clarithromycin AUC: ↑94% (↑75% ↑116%) Clarithromycin C_{max}: ↑50% (↑32% ↑71%) Clarithromycin C_{min}: ↑160% (↑135% ↑188%) 14-OH clarithromycin 14-OH clarithromycin AUC: ↓70% (↓74% ↓66%) 14-OH clarithromycin C_{max}: ↓72% (↓76% ↓67%) 14-OH clarithromycin C_{min}: ↓62% (↓66% ↓58%) Atazanavir AUC: ↑28% (↑16% ↑43%) Atazanavir C_{max}: ↔6% (↓7% ↑20%) Atazanavir C_{min}: ↑91% (↑66% ↑121%) A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.	No recommendation regarding dose reduction can be made; therefore, caution should be exercised if REYATAZ is co-administered with clarithromycin.
ANTIFUNGALS		
Ketoconazole 200 mg once daily (atazanavir 400 mg once daily)	No significant effect on atazanavir concentrations was observed.	Ketoconazole and itraconazole should be used cautiously with REYATAZ/ritonavir, high doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.
Itraconazole	Itraconazole, like ketoconazole, is a strong inhibitor as well as a substrate of CYP3A4.	
	Based on data obtained with other boosted PIs and ketoconazole, where ketoconazole AUC showed a 3-fold increase, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.	
Voriconazole 200 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) Subjects with at least one functional CYP2C19 allele.	Voriconazole AUC: ↓33% (↓42% ↓22%) Voriconazole C_{max}: ↓10% (↓22% ↓4%) Voriconazole C_{min}: ↓39% (↓49% ↓28%) Atazanavir AUC: ↓12% (↓18% ↓5%) Atazanavir C_{max}: ↓13% (↓20% ↓4%) Atazanavir C_{min}: ↓20% (↓28% ↓10%) Ritonavir AUC: ↓12% (↓17% ↓7%) Ritonavir C_{max}: ↓9% (↓17% ↔0%) Ritonavir C_{min}: ↓25% (↓35% ↓14%) In the majority of patients with at least one functional CYP2C19 allele, a reduction in both voriconazole and atazanavir exposures are expected.	Co-administration of voriconazole and REYATAZ with ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see section 4.4). At the time voriconazole treatment is required, a patient's CYP2C19 genotype should be performed if feasible. Therefore if the combination is

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Voriconazole 50 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) Subjects without a functional CYP2C19 allele.	Voriconazole AUC: ↑561% (↑451% ↑699%) Voriconazole C_{max}: ↑438% (↑355% ↑539%) Voriconazole C_{min}: ↑765% (↑571% ↑1,020%) Atazanavir AUC: ↓20% (↓35% ↓3%) Atazanavir C_{max}: ↓19% (↓34% ↔0.2%) Atazanavir C_{min}: ↓31% (↓46% ↓13%) Ritonavir AUC: ↓11% (↓20% ↓1%) Ritonavir C_{max}: ↓11% (↓24% ↑4%) Ritonavir C_{min}: ↓19% (↓35% ↑1%) In a small number of patients without a functional CYP2C19 allele, significantly increased voriconazole exposures are expected.	unavoidable, the following recommendations are made according to the CYP2C19 status: - in patients with at least one functional CYP2C19 allele, close clinical monitoring for a loss of both voriconazole (clinical signs) and atazanavir (virologic response) efficacy is recommended. - in patients without a functional CYP2C19 allele, close clinical and laboratory monitoring of voriconazole-associated adverse events is recommended. If genotyping is not feasible, full monitoring of safety and efficacy should be performed.
Fluconazole 200 mg once daily (atazanavir 300 mg and ritonavir 100 mg once daily)	Atazanavir and fluconazole concentrations were not significantly modified when REYATAZ/ritonavir was co-administered with fluconazole.	No dosage adjustments are needed for fluconazole and REYATAZ.
ANTIMYCOBACTERIAL		
Rifabutin 150 mg twice weekly (atazanavir 300 mg and ritonavir 100 mg once daily)	Rifabutin AUC: ↑48% (↑19% ↑84%)** Rifabutin C_{max}: ↑149% (↑103% ↑206%)** Rifabutin C_{min}: ↑40% (↑5% ↑87%)** 25-O-desacetyl-rifabutin AUC: ↑990% (↑714% ↑1 361%)** 25-O-desacetyl-rifabutin C_{max}: ↑677% (↑513% ↑883%)** 25-O-desacetyl-rifabutin C_{min}: ↑1 045% (↑715% ↑1 510%)** **When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC: ↑119% (↑78% ↑169%). In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.	When given with REYATAZ, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. 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. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for REYATAZ.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Rifampicin	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. During attempts to overcome the decreased exposure by increasing the dose of REYATAZ or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and REYATAZ is contraindicated (see section 4.3).
ANTIPSYCHOTICS		
Quetiapine	Due to CYP3A4 inhibition by REYATAZ, concentrations of quetiapine are expected to increase.	Co-administration of quetiapine with REYATAZ is contraindicated as REYATAZ may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see section 4.3).
Lurasidone	REYATAZ is expected to increase plasma levels of lurasidone due to CYP3A4 inhibition.	Co-administration of lurasidone with REYATAZ is contraindicated as this may increase lurasidone-related toxicity (see section 4.3).
ACID REDUCING AGENTS		
H_2-Receptor antagonists		
Without Tenofovir		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily		**For patients not taking tenofovir,** if REYATAZ 300 mg/ritonavir 100 mg and H_2-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg twice daily should not be exceeded. If a higher dose of an H_2-receptor antagonist is required (e.g., famotidine 40 mg twice daily or equivalent) an increase of the REYATAZ/ritonavir dose from 300/100 mg to 400/100 mg can be considered.
Famotidine 20 mg twice daily	Atazanavir AUC: ↓18% (↓25% ↑1%) Atazanavir C_{max}: ↓20% (↓32% ↓7%) Atazanavir C_{min}: ↔1% (↓16% ↑18%)	
Famotidine 40 mg twice daily	Atazanavir AUC: ↓23% (↓32% ↓14%) Atazanavir C_{max}: ↓23% (↓33% ↓12%) Atazanavir C_{min}: ↓20% (↓31% ↓8%)	
In healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg once daily		
Famotidine 40 mg twice daily	Atazanavir AUC: ↔3% (↓14% ↑22%) Atazanavir C_{max}: ↔2% (↓13% ↑8%) Atazanavir C_{min}: ↓14% (↓32% ↑8%)	
With Tenofovir disoproxil fumarate 300 mg once daily (equivalent to 245 mg tenofovir disoproxil)		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg once daily		**For patients who are taking tenofovir disoproxil fumarate,** if REYATAZ/ritonavir with both tenofovir disoproxil fumarate and an H_2-receptor antagonist are co-administered, a dose increase of REYATAZ to 400 mg with 100 mg of ritonavir is recommended. A dose equivalent to famotidine 40 mg twice daily should not be exceeded.
Famotidine 20 mg twice daily	Atazanavir AUC: ↓21% (↓34% ↓4%)* Atazanavir C_{max}: ↓21% (↓36% ↓4%)* Atazanavir C_{min}: ↓19% (↓37% ↑5%)*	
Famotidine 40 mg twice daily	Atazanavir AUC: ↓24% (↓36% ↓11%)* Atazanavir C_{max}: ↓23% (↓36% ↓8%)* Atazanavir C_{min}: ↓25% (↓47% ↑7%)*	
In HIV-infected patients with atazanavir/ritonavir at an increased dose of 400/100 mg once daily		
Famotidine 20 mg twice daily	Atazanavir AUC: ↑18% (↑6.5% ↑30%)* Atazanavir C_{max}: ↑18% (↑6.7% ↑31%)* Atazanavir C_{min}: ↑24% (↑10% ↑39%)*	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Famotidine 40 mg twice daily	Atazanavir AUC: ↔2.3% (↓13% ↑10%)* Atazanavir C_{max}: ↔5% (↓17% ↑8.4%)* Atazanavir C_{min}: ↔1.3% (↓10% ↑15)*	
	*When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg *without tenofovir disoproxil fumarate,,* atazanavir concentrations are expected to be additionally decreased by about 20%. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H_2-blockers.	
Proton pump inhibitors		
Omeprazole 40 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (am): 2 hr after omeprazole Atazanavir AUC: ↓61% (↓65% ↓55%) Atazanavir C_{max}: ↓66% (↓62% ↓49%) Atazanavir C_{min}: ↓65% (↓71% ↓59%)	Co-administration of REYATAZ with ritonavir and proton pump inhibitors is not recommended. If the combination is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of REYATAZ to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4).
Omeprazole 20 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily)	Atazanavir (am): 1 hr after omeprazole Atazanavir AUC: ↓30% (↓43% ↓14%)* Atazanavir C_{max}: ↓31% (↓42% ↓17%)* Atazanavir C_{min}: ↓31% (↓46% ↓12%)* *When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily. The decrease in AUC, C_{max}, and C_{min} was not mitigated when an increased dose of REYATAZ/ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.	
Antacids		
Antacids and medicinal products containing buffers	Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with REYATAZ.	REYATAZ should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by REYATAZ and/or ritonavir.	Co-administration of alfuzosin with REYATAZ is contraindicated (see section 4.3)

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTICOAGULANTS		
Direct-acting oral anticoagulants (DOACs)		
Apixaban **Rivaroxaban**	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.
Dabigatran	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.
Edoxaban	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. Please refer to the edoxaban SmPC sections 4.2 and 4.5 for appropriate edoxaban dosage recommendations for co-administration with P-gp inhibitors.
Vitamin K antagonists		
Warfarin	Co-administration with REYATAZ has the potential to increase or decrease warfarin concentrations.	It is recommended that the International Normalised Ratio (INR) be monitored carefully during treatment with REYATAZ, especially when commencing therapy.
ANTIEPILEPTICS		
Carbamazepine	REYATAZ may increase plasma levels of carbamazepine due to CYP3A4 inhibition. Due to carbamazepine inducing effect, a reduction in REYATAZ exposure cannot be ruled out.	Carbamazepine in combination with REYATAZ (with or without ritonavir) is contraindicated due to the risk for loss of virologic response and development of resistance (see section 4.3). Close monitoring of the patient's virologic response should be exercised.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Phenytoin, phenobarbital	Ritonavir may decrease plasma levels of phenytoin and/or phenobarbital due to CYP2C9 and CYP2C19 induction. Due to phenytoin/phenobarbital inducing effect, a reduction in REYATAZ exposure cannot be ruled out.	Phenobarbital and phenytoin in combination with REYATAZ (with or without ritonavir) are contraindicated due to the risk for loss of virologic response and development of resistance (see section 4.3). Close monitoring of patient's virologic response should be exercised.
Lamotrigine	Co-administration of lamotrigine and REYATAZ/ritonavir may decrease lamotrigine plasma concentrations due to UGT1A4 induction.	Lamotrigine should be used with caution in combination with REYATAZ/ritonavir. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly.
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		
Apalutamide	The mechanism of interaction is CYP3A4 induction by apalutamide and CYP3A4 inhibition by atazanavir/ritonavir.	Co-administration with REYATAZ (with or without ritonavir) is contraindicated due to the potential for decreased atazanavir and ritonavir plasma concentration with subsequent loss of virologic response and possible resistance to the class of protease inhibitors (see section 4.3). In addition, serum concentrations of apalutamide may be increased when coadministered with atazanavir/ritonavir, resulting in the potential for serious adverse events including seizure.
Encorafenib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of encorafenib with REYATAZ (with or without ritonavir) is contraindicated due to potential for loss of virologic response, development of resistance, increase in encorafenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Ivosidenib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of ivosidenib with REYATAZ (with or without ritonavir) is contraindicated due to potential for loss of virologic response, development of resistance, increase in ivosidenib plasma concentration and subsequent risk of serious adverse events such as QT interval prolongation (see section 4.3).
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If REYATAZ is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.
Immunosuppressants		
Cyclosporin **Tacrolimus** **Sirolimus**	Concentrations of these immunosuppressants may be increased when co-administered with REYATAZ due to CYP3A4 inhibition.	More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised.
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Amiodarone, **Systemic lidocaine,** **Quinidine**	Concentrations of these antiarrhythmics may be increased when co-administered with REYATAZ. The mechanism of amiodarone or systemic lidocaine/atazanavir interaction is CYP3A inhibition. Quinidine has a narrow therapeutic window and is contraindicated due to potential inhibition of CYP3A by REYATAZ.	Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3).
Calcium channel blockers		
Bepridil	REYATAZ should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil is contraindicated (see section 4.3)
Diltiazem 180 mg once daily (atazanavir 400 mg once daily)	Diltiazem AUC: ↑125% (↑109% ↑141%) Diltiazem C_{max}: ↑98% (↑78% ↑119%) Diltiazem C_{min}: ↑142% (↑114% ↑173%) Desacetyl-diltiazem AUC: ↑165% (↑145% ↑187%) Desacetyl-diltiazem C_{max}: ↑172% (↑144% ↑203%) Desacetyl-diltiazem C_{min}: ↑121% (↑102% ↑142%) No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem and REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition.	An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Verapamil	Serum concentrations of verapamil may be increased by REYATAZ due to CYP3A4 inhibition.	Caution should be exercised when verapamil is co-administered with REYATAZ.
CORTICOSTEROIDS		
Dexamethasone and other corticosteroids (all routes of administration)	Co-administration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of REYATAZ and development of resistance to atazanavir and/or ritonavir. Alternative corticosteroids should be considered. The mechanism of interaction is CYP3A4 induction by dexamethasone and CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration with corticosteroids (all routes of administration) that are metabolised by CYP3A, particularly for long-term use, may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. The potential benefit of treatment versus the risk of systemic corticosteroid effects should be considered. For co-administration of cutaneously administered corticosteroids sensitive to CYP3A inhibition, consult the Summary of Product Characteristics of the corticosteroid for condition or uses that augment its systemic absorption.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules twice daily) And **Inhaled/Nasal Corticosteroids**	The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82%-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway, e.g., budesonide. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition. Concomitant use of REYATAZ (with or without ritonavir) and other Inhaled/Nasal Corticosteroids is expected to produce the same effects.	Co-administration of REYATAZ/ritonavir and these glucocorticoids metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period. Concomitant use of Inhaled/Nasal Corticosteroids and REYATAZ (with or without ritonavir) may increase plasma concentrations of Inhaled/Nasal corticosteroids. Use with caution. Consider alternatives to Inhaled/Nasal Corticosteroids, particularly for long-term use.
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		
Sildenafil, tadalafil, vardenafil	Sildenafil, tadalafil, and vardenafil are metabolised by CYP3A4. Co-administration with REYATAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of this interaction is CYP3A4 inhibition.	Patients should be warned about these possible side effects when using PDE5 inhibitors for erectile dysfunction with REYATAZ (see section 4.4). Also see PULMONARY ARTERIAL HYPERTENSION in this table for further information regarding co-administration of REYATAZ with sildenafil.
GONADOTROPIN-RELEASING HORMONE (GnRH) RECEPTOR ANTAGONISTS		
Elagolix	The mechanism of interaction is anticipated increase in elagolix exposure in the presence of CYP3A4 inhibition by atazanavir and/or ritonavir.	Concomitant use of elagolix 200 mg twice daily with REYATAZ (with or without ritonavir) for more than 1 month is not recommended due to the potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily with REYATAZ (with or without ritonavir) to 6 months.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
KINASE INHIBITORS		
Fostamatinib	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Concomitant use of fostamatinib with REYATAZ (with or without ritonavir) may increase the plasma concentration of R406, the active metabolite of fostamatinib. Monitor for toxicities of R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.
HERBAL PRODUCTS		
St. John's wort (Hypericum perforatum)	Concomitant use of St. John's wort with REYATAZ may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3).	Co-administration of REYATAZ with products containing St. John's wort is contraindicated.
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol 25 µg + norgestimate (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Ethinyloestradiol AUC: ↓19% (↓25% ↓13%) Ethinyloestradiol C_{max}: ↓16% (↓26% ↓5%) Ethinyloestradiol C_{min}: ↓37% (↓45% ↓29%) Norgestimate AUC: ↑85% (↑67% ↑105%) Norgestimate C_{max}: ↑68% (↑51% ↑88%) Norgestimate C_{min}: ↑102% (↑77% ↑131%) While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side effects (e.g., insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	If an oral contraceptive is administered with REYATAZ/ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of REYATAZ/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Ethinyloestradiol 35 µg + norethindrone (atazanavir 400 mg once daily)	Ethinyloestradiol AUC: ↑48% (↑31% ↑68%) Ethinyloestradiol Cmax: ↑15% (↓1% ↑32%) Ethinyloestradiol Cmin: ↑91% (↑57% ↑133%) Norethindrone AUC: ↑110% (↑68% ↑162%) Norethindrone Cmax: ↑67% (↑42% ↑196%) Norethindrone Cmin: ↑262% (↑157% ↑409%) The increase in progestin exposure may lead to related side effects (e.g., insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	
LIPID-MODIFYING AGENTS		
HMG-CoA reductase inhibitors		
Simvastatin **Lovastatin**	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with REYATAZ may result in increased concentrations.	Co-administration of simvastatin or lovastatin with REYATAZ is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see section 4.3).
Atorvastatin	The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.	Co-administration of atorvastatin with REYATAZ is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring (see section 4.4).
Pravastatin **Fluvastatin**	Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9.	Caution should be exercised.
Other lipid-modifying agents		
Lomitapide	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 (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
INHALED BETA AGONISTS		
Salmeterol	Co-administration with REYATAZ may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of salmeterol with REYATAZ is not recommended (see section 4.4).
OPIOIDS		
Buprenorphine, once daily, stable maintenance dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Buprenorphine AUC: ↑67% Buprenorphine C_{max}: ↑37% Buprenorphine C_{min}: ↑69% Norbuprenorphine AUC: ↑105% Norbuprenorphine C_{max}: ↑61% Norbuprenorphine C_{min}: ↑101% The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir (when given with ritonavir) were not significantly affected.	Co-administration with REYATAZ with ritonavir warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Methadone, stable maintenance dose (atazanavir 400 mg once daily)	No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with REYATAZ, based on these data.	No dosage adjustment is necessary if methadone is co-administered with REYATAZ.
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		
Sildenafil	Co-administration with REYATAZ may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-inhibitor-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	A safe and effective dose in combination with REYATAZ has not been established for sildenafil when used to treat pulmonary arterial hypertension. Sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated (see section 4.3).

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
SEDATIVES		
Benzodiazepines		
Midazolam **Triazolam**	Midazolam and triazolam are extensively metabolised by CYP3A4. Co-administration with REYATAZ may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of REYATAZ with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4-fold increase in midazolam plasma levels.	Co-administration of REYATAZ with triazolam or orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co-administration of REYATAZ and parenteral midazolam. If REYATAZ is co-administered with parenteral 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data in pregnant women (between 300-1 000 pregnancy outcomes) indicate no malformative toxicity of atazanavir. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of REYATAZ may be considered during pregnancy only if the potential benefit justifies the potential risk.

In clinical trial AI424-182 REYATAZ/ritonavir (300/100 mg or 400/100 mg) in combination with zidovudine/lamivudine was administered to 41 pregnant women during the second or third trimester. Six of 20 (30%) women on REYATAZ/ritonavir 300/100 mg and 13 of 21 (62%) women on REYATAZ/ritonavir 400/100 mg experienced grades 3 to 4 hyperbilirubinaemia. There were no cases of lactic acidosis observed in the clinical trial AI424-182.

The study assessed 40 infants who received antiretroviral prophylactic treatment (which did not include REYATAZ) and were negative for HIV-1 DNA at the time of delivery and/or during the first 6 months postpartum. Three of 20 infants (15%) born to women treated with REYATAZ/ritonavir 300/100 mg and four of 20 infants (20%) born to women treated with REYATAZ/ritonavir 400/100 mg experienced grade 3-4 bilirubin. There was no evidence of pathologic jaundice and six of 40 infants in this study received phototherapy for a maximum of 4 days. There were no reported cases of kernicterus in neonates.

For dosing recommendations see section 4.2 and for pharmacokinetic data see section 5.2.

It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring should be considered.

Breast-feeding

Atazanavir has been detected in human milk. In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

In a nonclinical fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with regimens containing REYATAZ (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

REYATAZ has been evaluated for safety in combination therapy with other antiretroviral medicinal products in controlled clinical trials in 1,806 adult patients receiving REYATAZ 400 mg once daily (1,151 patients, 52 weeks median duration and 152 weeks maximum duration) or REYATAZ 300 mg with ritonavir 100 mg once daily (655 patients, 96 weeks median duration and 108 weeks maximum duration).

Adverse reactions were consistent between patients who received REYATAZ 400 mg once daily and patients who received REYATAZ 300 mg with ritonavir 100 mg once daily, except that jaundice and elevated total bilirubin levels were reported more frequently with REYATAZ plus ritonavir.

Among patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a possible relationship to regimens containing REYATAZ and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving REYATAZ 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%. In the majority of cases, jaundice was reported within a few days to a few months after the initiation of treatment (see section 4.4).

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown 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 (see section 4.4).

Tabulated list of adverse reactions

Assessment of adverse reactions for REYATAZ is based on safety data from clinical studies and post-marketing experience. Frequency is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:	uncommon: hypersensitivity
Metabolism and nutrition disorders:	uncommon: weight decreased, weight gain, anorexia, appetite increased
Psychiatric disorders:	uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream
Nervous system disorders:	common: headache; uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia
Eye disorders:	common: ocular icterus
Cardiac disorders:	uncommon: torsades de pointes[a] rare: QTc prolongation[a], oedema, palpitation
Vascular disorders:	uncommon: hypertension
Respiratory, thoracic and mediastinal disorders:	uncommon: dyspnoea
Gastrointestinal disorders:	common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia; uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth
Hepatobiliary disorders:	common: jaundice; uncommon: hepatitis, cholelithiasis[a], cholestasis[a]; rare: hepatosplenomegaly, cholecystitis[a]
Skin and subcutaneous tissue disorders:	common: rash; uncommon: erythema multiforme[a,b], toxic skin eruptions[a,b], drug rash with eosinophilia and systemic symptoms (DRESS) syndrome[a,b], angioedema[a], urticaria, alopecia, pruritus; rare: Stevens-Johnson syndrome[a,b], vesiculobullous rash, eczema, vasodilatation
Musculoskeletal and connective tissue disorders:	uncommon: muscle atrophy, arthralgia, myalgia; rare: myopathy
Renal and urinary disorders:	uncommon: nephrolithiasis, haematuria, proteinuria, pollakiuria, interstitial nephritis, chronic kidney disease[a]; rare: kidney pain
Reproductive system and breast disorders:	uncommon: gynaecomastia
General disorders and administration site conditions:	common: fatigue; uncommon: chest pain, malaise, pyrexia, asthenia; rare: gait disturbance

[a] These adverse reactions were identified through post-marketing surveillance, however, the frequencies were estimated from a statistical calculation based on the total number of patients exposed to REYATAZ in randomised controlled and other available clinical trials (n = 2 321).
[b] See description of selected adverse reactions for more details.

Description of selected adverse reactions

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Rash and associated syndromes
Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with the use of REYATAZ (see section 4.4).

Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naïve patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations.

Paediatric population

In a clinical study AI424-020, paediatric patients 3 months to less than 18 years of age who received either the oral powder or capsule formulation had a mean duration of treatment with REYATAZ of 115 weeks. The safety profile in this study was overall comparable to that seen in adults. Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. The most frequently reported laboratory abnormalities in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4) which occurred in 45% of patients.

In clinical studies AI424-397 and AI424-451, paediatric patients 3 months to less than 11 years of age had a mean duration of treatment with REYATAZ oral powder of 80 weeks. No deaths were reported. The safety profile in these studies was overall comparable to that seen in previous paediatric and adult studies. The most frequently reported laboratory abnormalities in paediatric patients receiving REYATAZ oral powder was elevation of total bilirubin (≥ 2.6 times ULN, Grade 3-4; 16%) and increased amylase (Grade 3-4; 33%), generally of non-pancreatic origin. Elevation in ALT levels were more frequently reported in paediatric patients in these studies than in adults.

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus
Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).

Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE08

Mechanism of action
Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Resistance

Antiretroviral treatment naïve adult patients
In clinical trials of antiretroviral treatment-naïve patients treated with unboosted atazanavir, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. Resistance levels to atazanavir ranged from 3.5- to 29-fold without evidence of phenotypic cross resistance to other PIs. In clinical trials of antiretroviral treatment-naïve patients treated with boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

Table 3: De novo substitutions in treatment-naïve patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)

Frequency	de novo PI substitution (n = 26)[a]
> 20%	none
10-20%	none

[a] Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/mL).

The M184I/V substitution emerged in 5/26 REYATAZ/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients
In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naïve patients.

Table 4: De novo substitutions in treatment experienced patients failing therapy with atazanavir + ritonavir (Study 045, 48 weeks)

Frequency	de novo PI substitution (n = 35)[a,b]
> 20%	M36, M46, I54, A71, V82
10-20%	L10, I15, K20, V32, E35, S37, F53, I62, G73, I84, L90

[a] Number of patients with paired genotypes classified as virological failures (HIV RNA ≥ 400 copies/mL).
[b] Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]> 5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA)

None of the de novo substitutions (see Table 4) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in Study 045 treatment-experienced population.

The resistance in antiretroviral treatment experienced patients mainly occurs by accumulation of the major and minor resistance substitutions described previously to be involved in protease inhibitor resistance.

Clinical results

In antiretroviral naïve adult patients
Study 138 is an international randomised, open-label, multicenter, prospective trial of 883 antiretroviral treatment-naïve patients comparing REYATAZ/ritonavir (300 mg/100 mg once daily) to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed-dose tenofovir disoproxil fumarate/emtricitabine (300 mg/200 mg tablets once daily). The REYATAZ/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/mL at Week 48 (Table 5).

Analyses of data through 96 weeks of treatment demonstrated durability of antiviral activity (Table 5).

The mean baseline CD4 cell count was 214 cells/mm^3 (range: 2 to 810 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.94 log_{10} copies/mL (range: 2.6 to 5.88 log_{10} copies/mL). The REYATAZ/ritonavir arm has similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, as assessed by the proportion of patients with HIV RNA < 50 copies/mL at Week 48: 78% of patients on REYATAZ/ritonavir compared to 76% on lopinavir/ritonavir (difference estimate of ATV/RTV-LPV/RTV: 1.7% [95% CI, -3.8%, 7.1%] according to the Confirmed Virologic Response (CVR) Non-Completer = Failure (NC = F) definition of response.

In a per protocol analysis which excluded non-completers (i.e., patients who discontinued before the Week 48 HIV RNA assessment) and patients with major protocol deviations, the proportion of patients with HIV RNA < 50 copies/mL at Week 48 was 86% (338/392) for REYATAZ/ritonavir and 89% (332/372) for lopinavir/ritonavir (difference estimate of ATV/RTV-LPV/RTV: -3% [95% CI, -7.6%, 1.5%].

Table 5: Efficacy Outcomes in Study 138[a]

Parameter	**REYATAZ/ritonavir[b] (300 mg/100 mg once daily) n = 440**		**Lopinavir/ritonavir[c] (400 mg/100 mg twice daily) n = 443**	
	Week 48	**Week 96**	**Week 48**	**Week 96**
HIV RNA < 50 copies/mL, %				
All patients[d]	78	74	76	68
Difference estimate [95% CI][d]	Week 48: 1.7% [-3.8%, 7.1%] Week 96: 6.1% [0.3%, 12.0%]			
Per protocol analysis[e]	86 (n = 392[f])	91 (n = 352)	89 (n = 372)	89 (n = 331)
Difference estimate[e] [95% CI]	Week 48: -3% [-7.6%, 1.5%] Week 96: 2.2% [-2.3%, 6.7%]			
HIV RNA < 50 copies/mL, % by Baseline Characteristic[d]				
HIV RNA < 100,000 copies/mL	82 (n = 217)	75 (n = 217)	81 (n = 218)	70 (n = 218)
≥ 100,000 copies/mL	74 (n = 223)	74 (n = 223)	72 (n = 225)	66 (n = 225)
CD4 count < 50 cells/mm^3	78 (n = 58)	78 (n = 58)	63 (n = 48)	58 (n = 48)
50 to < 100 cells/mm^3	76 (n = 45)	71 (n = 45)	69 (n = 29)	69 (n = 29)
100 to < 200 cells/mm^3	75 (n = 106)	71 (n = 106)	78 (n = 134)	70 (n = 134)
≥ 200 cells/mm^3	80 (n = 222)	76 (n = 222)	80 (n = 228)	69 (n = 228)
HIV RNA Mean Change from Baseline, log_{10} copies/mL				
All patients	-3.09 (n = 397)	-3.21 (n = 360)	-3.13 (n = 379)	-3.19 (n = 340)
CD4 Mean Change from Baseline, cells/mm^3				
All patients	203 (n = 370)	268 (n = 336)	219 (n = 363)	290 (n = 317)
CD4 Mean Change from Baseline, cells/mm^3 by Baseline Characteristic				
HIV RNA < 100,000 copies/mL	179 (n = 183)	243 (n = 163)	194 (n = 183)	267 (n = 152)
≥ 100,000 copies/mL	227 (n = 187)	291 (n = 173)	245 (n = 180)	310 (n = 165)

[a] Mean baseline CD4 cell count was 214 cells/mm^3 (range 2 to 810 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.94 log_{10} copies/mL (range 2.6 to 5.88 log_{10} copies/mL)
[b] REYATAZ/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[c] Lopinavir/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[d] Intent-to-treat analysis, with missing values considered as failures.
[e] Per protocol analysis: Excluding non-completers and patients with major protocol deviations.
[f] Number of patients evaluable.

In antiretroviral experienced adult patients
Study 045 is a randomised, multicenter trial comparing REYATAZ/ritonavir (300/100 mg once daily) and REYATAZ/saquinavir (400/1,200 mg once daily), to lopinavir + ritonavir (400/100 mg fixed-dose combination twice daily), each in combination with tenofovir disoproxil fumarate (see sections 4.5 and 4.8) and one NRTI, in patients with virologic failure on two or more prior regimens containing at least one PI, NRTI, and NNRTI. For randomised patients, the mean time of prior antiretroviral exposure was 138 weeks for PIs, 281 weeks for NRTIs, and 85 weeks for NNRTIs. At baseline, 34% of patients were receiving a PI and 60% were receiving an NNRTI. Fifteen of 120 (13%) patients in the REYATAZ + ritonavir treatment arm and 17 of 123 (14%) patients in the lopinavir + ritonavir arm

had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients in the study had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through 48 weeks (Table 6).

Table 6: Efficacy Outcomes at Week 48[a] and at Week 96 (Study 045)

Parameter	ATV/RTV[b] (300 mg/100 mg once daily) n = 120		LPV/RTV[c] (400 mg/100 mg twice daily) n = 123		Time-averaged difference ATV/RTV-LPV/RTV [97.5% CI[d]]	
	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
HIV RNA Mean Change from Baseline, log_{10} copies/mL						
All patients	-1.93 (n = 90[e])	-2.29 (n = 64)	-1.87 (n = 99)	-2.08 (n = 65)	0.13 [-0.12, 0.39]	0.14 [-0.13, 0.41]
HIV RNA < 50 copies/mL, %[f] (responder/evaluable)						
All patients	36 (43/120)	32 (38/120)	42 (52/123)	35 (41/118)	NA	NA
HIV RNA < 50 copies/mL by select baseline PI substitutions,[f, g] % (responder/evaluable)						
0-2	44 (28/63)	41 (26/63)	56 (32/57)	48 (26/54)	NA	NA
3	18 (2/11)	9 (1/11)	38 (6/16)	33 (5/15)	NA	NA
≥ 4	27 (12/45)	24 (11/45)	28 (14/50)	20 (10/49)	NA	NA
CD4 Mean Change from Baseline, cells/mm^3						
All patients	110 (n = 83)	122 (n = 60)	121 (n = 94)	154 (n = 60)	NA	NA

[a] The mean baseline CD4 cell count was 337 cells/mm^3 (range: 14 to 1,543 cells/mm^3) and the mean baseline plasma HIV-1 RNA level was 4.4 log_{10} copies/mL (range: 2.6 to 5.88 log_{10} copies/mL).
[b] ATV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[c] LPV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed-dose 300 mg/200 mg tablets once daily).
[d] Confidence interval.
[e] Number of patients evaluable.
[f] Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/mL were 53% and 43% for ATV/RTV and 54% and 46% for LPV/RTV at Weeks 48 and 96 respectively.
[g] Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.
NA = not applicable.

Through 48 weeks of treatment, the mean changes from baseline in HIV RNA levels for REYATAZ + ritonavir and lopinavir + ritonavir were similar (non-inferior). Consistent results were obtained with the last observation carried forward method of analysis (time-averaged difference of 0.11, 97.5% confidence interval [-0.15, 0.36]). By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/mL (< 50 copies/mL) in the REYATAZ + ritonavir arm and the lopinavir + ritonavir arm were 55% (40%) and 56% (46%), respectively.

Through 96 weeks of treatment, mean HIV RNA changes from baseline for REYATAZ + ritonavir and lopinavir + ritonavir met criteria for non-inferiority based on observed cases. Consistent results were obtained with the last observation carried forward method of analysis. By as-treated analysis, excluding missing values, the proportions of patients with HIV RNA < 400 copies/mL (< 50 copies/mL) for REYATAZ + ritonavir were 84% (72%) and for lopinavir + ritonavir were 82% (72%). It is important to note that at time of the 96-week analysis, 48% of patients overall remained on study.

REYATAZ + saquinavir was shown to be inferior to lopinavir + ritonavir.

Paediatric population

Paediatric trials with REYATAZ capsules
Assessment of the pharmacokinetics, safety, tolerability, and efficacy of REYATAZ is based on data from the open-label, multicenter clinical trial AI424-020 conducted in patients from 3 months to 21 years of age. Overall in this study, 182 paediatric patients (81 antiretroviral-naïve and 101 antiretroviral-experienced) received once daily REYATAZ (capsule or powder formulation), with or without ritonavir, in combination with two NRTIs.

The clinical data derived from this study are inadequate to support the use of atazanavir capsules (with or without ritonavir) in children below 6 years of age.

Efficacy data observed in the 41 paediatric patients aged 6 years to less than 18 years that received REYATAZ capsules with ritonavir are presented in Table 7. For treatment-naïve paediatric patients, the mean baseline CD4 cell count was 344 cells/mm^3 (range: 2 to 800 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.67 log_{10} copies/mL (range: 3.70 to 5.00 log_{10} copies/mL). For treatment experienced paediatric patients, the mean baseline CD4 cell count was 522 cells/mm^3 (range: 100 to 1157 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.09 log_{10} copies/mL (range: 3.28 to 5.00 log_{10} copies/mL).

Table 7: Efficacy Outcomes (paediatric patients 6 years to less than 18 years of age) at Week 48 (Study AI424-020)

Parameter	Treatment-Naïve REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n = 16	Treatment-Experienced REYATAZ Capsules/ritonavir (300 mg/100 mg once daily) n = 25
HIV RNA < 50 copies/mL, %[a]		
All patients	81 (13/16)	24 (6/25)
HIV RNA < 400 copies/mL, %[a]		
All patients	88 (14/16)	32 (8/25)
CD4 Mean Change from Baseline, cells/mm^3		
All patients	293 (n = 14[b])	229 (n = 14[b])
HIV RNA < 50 copies/mL by select baseline PI substitutions,[c] % (responder/evaluable[d])		
0-2	NA	27 (4/15)
3	NA	-
≥ 4	NA	0 (0/3)

[a] Intent-to-treat analysis, with missing values considered as failures.
[b] Number of patients evaluable.
[c] PI major L24I, D30N, V32I, L33F, M46IL, I47AV, G48V, I50LV, F53LY, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M; PI minor: L10CFIRV, V11I, E35G, K43T, Q58E, A71ILTV, G73ACST, T74P, N83D, L89V.
[d] Includes patients with baseline resistance data.
NA = not applicable.

Paediatric trials with REYATAZ oral powder
Assessment of the pharmacokinetics, safety, tolerability, and virologic response of REYATAZ oral powder was based on data from two open-label, multicenter clinical trials.
- AI424-397 (PRINCE I): In paediatric patients from 3 months to less than 6 years of age
- AI424-451 (PRINCE II): In paediatric patients from 3 months to less than 11 years of age

In these studies, 155 patients (59 antiretroviral-naïve and 96 antiretroviral-experienced) received once daily REYATAZ oral powder and ritonavir, in combination with two NRTIs.

For inclusion in both trials, treatment-naïve patients had to have genotypic sensitivity to REYATAZ and two NRTIs, and treatment-experienced patients had to have documented genotypic and phenotypic

sensitivity at screening to REYATAZ and at least 2 NRTIs. Patients exposed only to antiretrovirals *in utero* or intrapartum were considered treatment-naïve. Patients who received REYATAZ or REYATAZ/ritonavir at any time prior to study enrollment or who had a history of treatment failure on two or more protease inhibitors, protease inhibitor resistance or evidence of pre-existing cardiac abnormalities were excluded from the trials. Protease inhibitor resistance was defined as genotypic resistance to atazanavir or either component of the local NRTI backbone based on the criteria of 1) any major mutations: I50L, I84V, N88S and 2) ≥ 2 of the following minor or cross resistant mutations: M46I/L, G48V, I54L/V/M/T/A, V82A/T/FI, L90M, V32I.

At Week 48 there were 134 paediatric patients aged 3 months to less than 11 years that received REYATAZ oral powder with ritonavir that were evaluated for efficacy. These data are presented in Table 8. For treatment-naïve paediatric patients, the mean baseline CD4 cell count was 930 cells/mm^3 (range: 46 to 2291 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.81 log_{10} copies/mL (range: 3.4 to 5.9 log_{10} copies/mL). For treatment-experienced paediatric patients, the mean baseline CD4 cell count was 1441 cells/mm^3 (range: 84 to 5703 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.67 log_{10} copies/mL (range: 2.0 to 5.9 log_{10} copies/mL).

Table 8: Efficacy Outcomes for oral powder (paediatric patients at least 3 months of age and weighing at least 5 kg) at Week 48 (Studies AI424-397 and AI424-451)

Parameter	Treatment-Naïve REYATAZ Powder/ritonavir n = 52	Treatment-Experienced REYATAZ Powder/ritonavir n = 82
HIV RNA < 50 copies/mL, %[a]		
at least 5 to < 10 kg (REYATAZ 150 and 200 mg)	33 (4/12)	52 (17/33)
at least 10 to < 15 kg	59 (13/22)	35 (6/17)
at least 15 to < 25 kg	61 (11/18)	57 (17/30)
at least 25 to < 35 kg	-	50.0 (1/2)
HIV RNA < 400 copies/mL, %[a]		
at least 5 to < 10 kg (REYATAZ 150 and 200 mg)	75 (9/12)	61 (20/33)
at least 10 to < 15 kg	82 (18/22)	59 (10/17)
at least 15 to < 25 kg	78 (14/18)	67 (20/30)
at least 25 to < 35 kg	-	50.0 (1/2)
CD4 Mean Change from Baseline, cells/mm^3		
at least 5 to < 10 kg (REYATAZ 150 and 200 mg)	293 (n = 7)	63 (n = 16)
at least 10 to < 15 kg	293 (n = 11)	307 (n = 8)
at least 15 to < 25 kg	305 (n = 9)	374 (n = 12)
at least 25 to < 35 kg	-	213 (n = 1)

[a] Intent-to-treat analysis, with missing values considered as failures.

5.2 Pharmacokinetic properties

Absorption: in HIV-infected patients (n = 33, combined studies), multiple dosing of REYATAZ 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/mL, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/mL and 44185 (51%) ng•h/mL, respectively.

Food effect: co-administration of REYATAZ and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately

33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high-fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, REYATAZ is to be taken with food.

Distribution: atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/mL. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/mL). In a multiple-dose study in HIV-infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

Metabolism: studies in humans and *in vitro* studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised. Neither metabolite demonstrated *in vitro* antiviral activity.

Elimination: following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n = 33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

Linearity/non-linearity: the pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition.

Special populations

Renal impairment: in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n = 20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown (see sections 4.2 and 4.4.).

Hepatic impairment: atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

Age/Gender: a study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

Race: a population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.

Pregnancy:
The pharmacokinetic data from HIV-infected pregnant women receiving REYATAZ capsules with ritonavir are presented in Table 9.

Table 9: Steady-State Pharmacokinetics of Atazanavir with ritonavir in HIV-Infected Pregnant Women in the Fed State

	atazanavir 300 mg with ritonavir 100 mg		
Pharmacokinetic Parameter	**2nd Trimester** (n = 9)	**3rd Trimester** (n = 20)	**postpartum**[a] (n = 36)
C_{max} ng/mL Geometric mean (CV%)	3 729.09 (39)	3 291.46 (48)	5 649.10 (31)
AUC ng•h/mL Geometric mean (CV%)	34 399.1 (37)	34 251.5 (43)	60 532.7 (33)
C_{min} ng/mL[b] Geometric mean (CV%)	663.78 (36)	668.48 (50)	1 420.64 (47)

[a] Atazanavir peak concentrations and AUCs were found to be approximately 26-40% higher during the postpartum period (4-12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2-fold higher during the postpartum period when compared to those observed historically in HIV-infected non-pregnant patients.
[b] C_{min} is concentration 24 hours post-dose.

Paediatric population
There is a trend toward a higher clearance in younger children when normalised for body weight. As a result, greater peak to trough ratios are observed; however at recommended doses, geometric mean atazanavir exposures (C_{min}, C_{max}, and AUC) in paediatric patients are expected to be similar to those observed in adults.

5.3 Preclinical safety data

In repeat-dose toxicity studies, conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis. Systemic exposures of atazanavir in mice (males), rats, and dogs at doses associated with hepatic changes were at least equal to that observed in humans given 400 mg once daily. In female mice, atazanavir exposure at a dose that produced single-cell necrosis was 12 times the exposure in humans given 400 mg once daily. Serum cholesterol and glucose were minimally to mildly increased in rats but not in mice or dogs.

During *in vitro* studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at C_{max} in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD_{90}) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In pregnant rabbits, gross lesions of the stomach and intestines were observed in dead or moribund does at maternal doses 2 and 4 times the highest dose administered in the definitive embryo-development study. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic activation. In *in vivo* studies in rats, atazanavir

did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic *in vitro*.

In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. The increased incidence of benign hepatic adenomas in female mice was likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Atazanavir increased opacity of bovine corneas in an *in vitro* ocular irritation study, indicating it may be an ocular irritant upon direct contact with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Sucrose
Orange vanilla flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After mixing with food or beverage, mixture may be stored for up to 1 hour at temperatures not above 30°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

REYATAZ oral powder should be stored in the original sachet and should not be opened until ready to use.

For storage conditions after mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Polyester film/Aluminum/Polyethylene sealant film sachet.

Each carton contains 30 sachets.

6.6 Special precautions for disposal and other handling

Instructions for use:
The dose and the number of REYATAZ oral powder sachets needed is determined based on weight (see section 4.2.).

1. Prior to mixing, the sachet is tapped to settle the powder. A clean pair of scissors is used to cut each sachet along the dotted line.
2. The appropriate option listed below is chosen for mixing and administration with liquid infant formula, beverage or food. Larger volumes or quantities of liquid infant formula, beverage or

food may be used for dosing. It should be ensured that the patient eats or drinks all the infant formula, beverage or food that contains the powder.

A: To mix the recommended number of REYATAZ oral powder sachets with liquid infant formula in a small medicine cup or small container and to administer with an oral syringe, which can be obtained from a pharmacist:
- A spoon is used to mix the content of the appropriate number of sachets (4 or 5 sachets depending on infant weight) with 10 mL of prepared liquid infant formula in the medicine cup or small container. The full amount of the mixture is drawn up into an oral syringe and administered into either right or left inner cheek of the infant. Another 10 mL of formula is poured into the medicine cup or small container to rinse off remaining REYATAZ oral powder in the cup or container. The residual mixture is drawn up into the syringe and administered into either the right or left inner cheek of the infant.

B: To mix the recommended number of REYATAZ oral powder sachets with a beverage such as milk or water in a small drinking cup:
- A spoon is used to mix the content of the sachets with 30 mL of the beverage. The child is to drink the mixture. An additional 15 mL of beverage is added to the drinking cup for thorough rinsing of the cup and contents are mixed. The child is to drink the entire residual mixture.
- If water is used, food should also be taken at the same time.

C: To mix the recommended number of REYATAZ oral powder sachets with food such as applesauce or yogurt in a small container:
- One tablespoon of food is used to mix the content of the sachets. The mixture is fed to the infant or young child. An additional tablespoon of food is added to the small container for thorough delivery of the powder from the container and contents are mixed. The entire residual mixture is fed to the child.

3. The entire dosage of REYATAZ oral powder (mixed in the liquid infant formula, beverage or food) is administered within one hour of preparation (the mixture can be left at room stored at temperatures not above 30°C during this period).
4. Additional infant formula, beverage or food may be given after consumption of the entire mixture.
5. Ritonavir is administered immediately following REYATAZ powder administration.

For further details on the preparation and administration of the REYATAZ oral powder, see the Patient Information Leaflet, Instructions for Use section

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 2004
Date of latest renewal: 06 February 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
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Shannon, Co. Clare, V14 DD39
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg of atazanavir (as sulphate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Carton Bottle pack: (1 bottle): 60 hard capsules
Carton Bottle pack: (3 bottles): 3 x 60 hard capsules (3 bottles of 60 hard capsules)
Label Bottle pack: 60 hard capsules

Blister pack: 60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Capsules should be swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Bottle pack:
Do not store above 25°C.

Blister pack:
Do not store above 25°C.
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

Bottle pack:
60 hard capsules: EU/1/03/267/005
3 x 60 hard capsules: EU/1/03/267/011

Blister pack:
60 hard capsules: EU/1/03/267/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 200 mg hard capsules
atazanavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT (BOTTLE AND BLISTER PRESENTATIONS) AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 300 mg hard capsules
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 300 mg of atazanavir (as sulphate).

3. LIST OF EXCIPIENTS

Excipients: contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Carton Bottle pack: (1 bottle): 30 hard capsules
Carton Bottle pack: (3 bottles): 3 x 30 hard capsules (3 bottles of 30 hard capsules)
Label Bottle pack: 30 hard capsules

Blister pack: 30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Capsules should be swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Bottle pack:
Do not store above 25°C.

Blister pack:
Do not store above 25°C.
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

Bottle pack:
30 hard capsules: EU/1/03/267/008
3 x 30 hard capsules: EU/1/03/267/010

Blister pack:
30 hard capsules: EU/1/03/267/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 300 mg hard capsules
atazanavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

REYATAZ 50 mg oral powder
atazanavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 50 mg of atazanavir (as sulphate).

3. LIST OF EXCIPIENTS

Contains aspartame and sucrose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Oral Powder
30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/267/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: REYATAZ 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

REYATAZ 50 mg ORAL POWDER - FOIL SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

REYATAZ 50 mg oral powder
Atazanavir
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

REYATAZ 200 mg hard capsules
atazanavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What REYATAZ is and What it is used for

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called *protease inhibitors*. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

REYATAZ capsules may be used by adults and children 6 years of age and older. Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

2. What you need to know before you take REYATAZ

Do not take REYATAZ

- **if you are allergic** to atazanavir or any of the other ingredients of this medicine (listed in section 6)
- **if you have moderate to severe liver problems.** Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- **if you are taking any of these medicines:** see also *Other medicines and REYATAZ*
  - rifampicin (an antibiotic used to treat tuberculosis)
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches); and alfuzosin (used to treat enlarged prostatic gland)
  - quetiapine (used to treat schizophrenia, bipolar disorder, and major depressive disorder); lurasidone (used to treat schizophrenia)
  - medicines containing St. John’s wort *(Hypericum perforatum*, an herbal preparation)

- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety)
- lomitapide, simvastatin, and lovastatin (used to lower blood cholesterol)
- grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination, and glecaprevir/pibrentasvir fixed-dose combination (used to treat chronic hepatitis C infection)
- apalutamide (used to treat prostate cancer), encorafenib (used to treat cancer) and ivosidenib (used to treat cancer)
- carbamazepine, phenobarbital, and phenytoin (used to treat seizures)

Do not take sildenafil with REYATAZ when sildenafil is used for the treatment of pulmonary arterial hypertension. Sildenafil is also used for the treatment of erectile dysfunction. Tell your doctor if you are using sildenafil for the treatment of erectile dysfunction.

Tell your doctor at once if any of these apply to you.

Warnings and precautions

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection.

Some people will need special care before or while taking REYATAZ. Talk to your doctor or pharmacist before taking REYATAZ and make sure your doctor knows:

- if you have hepatitis B or C
- if you develop signs or symptoms of gall stones (pain at the right side of your stomach)
- if you have type A or B haemophilia
- if you require haemodialysis

REYATAZ may affect how well your kidneys work.

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in hands and feet and moving up towards the trunk of the body, palpitations, tremor, or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder), and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

Serious skin rash, including Stevens-Johnson syndrome, has been reported in patients taking REYATAZ. If you develop a rash inform your doctor immediately.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor. Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

Children

Do not give this medicine to children younger than 3 months of age and weighing less than 5 kg. The use of REYATAZ in children less than 3 months of age and weighing less than 5 kg has not been studied due to the risk of serious complications.

Other medicines and REYATAZ

You must not take REYATAZ with certain medicines. These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking, have recently taken, or might take any other medicines. It is especially important to mention these:

- other medicines to treat HIV infection (e.g., indinavir, nevirapine, and efavirenz)
- sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C)
- sildenafil, vardenafil, or tadalafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive (**"the Pill"**) with REYATAZ to prevent pregnancy, be sure to take it exactly as instructed by your doctor and not miss any doses
- any medicines used to treat diseases related to the acid in the stomach (e.g., antacids to be taken 1 hour before taking REYATAZ or 2 hours after taking REYATAZ, H_2-blockers like famotidine and proton pump inhibitors like omeprazole)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm (amiodarone, diltiazem, systemic lidocaine, verapamil)
- atorvastatin, pravastatin, and fluvastatin (used to lower blood cholesterol)
- salmeterol (used to treat asthma)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, clopidogrel, prasugrel, and ticagrelor (used to reduce blood clots)
- lamotrigine (antiepileptic)
- irinotecan (used to treat cancer)
- elagolix (gonadotropin-releasing hormone receptor antagonists, used to treat severe pain from endometriosis)
- fostamatinib (used to treat chronic immune thrombocytopenia)
- sedative agents (e.g., midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain)
- corticosteroids (all routes of administration; including dexamethasone).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking an inhaled or nasal (given in the nose) corticosteroid, including fluticasone or budesonide (given to treat allergic symptoms or asthma).

REYATAZ with food and drink

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

Pregnancy and breast-feeding

If you are pregnant or think that you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Atazanavir, the active substance of REYATAZ, is excreted in human milk. Patients should not breast-feed while taking REYATAZ.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***.

Driving and using machines

If you feel dizzy or lightheaded, do not drive or use machines and contact your doctor immediately.

REYATAZ contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars (e.g., lactose), contact your doctor before taking this medicinal product.

3. How to take REYATAZ

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

The recommended adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food, in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:

Body Weight (kg)	**REYATAZ Dose once daily (mg)**	**Ritonavir Dose* once daily (mg)**
15 to less than 35	200	100
at least 35	300	100

*Ritonavir capsules, tablets, or oral solution may be used.

REYATAZ is also available as an oral powder for use in children at least 3 months old and weighing at least 5 kg. Switching to REYATAZ capsules from REYATAZ oral powder is encouraged as soon as patients are able to consistently swallow capsules.

A change in dose may occur when switching between oral powder and capsules. Your doctor will decide the right dose based on your child’s weight.

There are no dosing recommendations for REYATAZ in paediatric patients less than 3 months of age.

Take REYATAZ capsules with food (a meal or a substantial snack). Swallow the capsules whole. **Do not open the capsules.**

If you take more REYATAZ than you should

Yellowing of the skin and/or eyes (jaundice) and irregular heartbeat (QTc prolongation) may occur if you or your child take too much REYATAZ.
If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

If you forget to take REYATAZ

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking REYATAZ

Do not stop taking REYATAZ before talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Tell your doctor immediately if you develop any of the following serious side effects:

- Skin rash, itching that may occasionally be severe has been reported. The rash usually disappears within 2 weeks without any change to your REYATAZ treatment. Severe rash may be developed in association with other symptoms which could be serious. Stop taking REYATAZ and talk to your doctor immediately if you develop a severe rash or a rash with flu-like illness symptoms, blisters, fever, mouth sores, muscle or joint pain, swelling in the face, inflammation of the eye which causes redness (conjunctivitis), painful, warm, or red lumps (nodules).
- Yellowing of your skin or the white part of your eyes caused by high levels of bilirubin in your blood has been commonly reported. This side effect is usually not dangerous in adults and infants older than 3 months of age; but it might be a symptom of a serious problem. If your skin or the white part of your eyes turns yellow, talk to your doctor immediately.
- Changes in the way your heart beats (heart rhythm change) may occasionally happen. Talk to your doctor immediately if you get dizzy, lightheaded or if you suddenly faint. These could be symptoms of a serious heart problem.
- Liver problems may uncommonly happen. Your doctor should do blood tests prior you start REYATAZ and during treatment. If you have liver problems, including hepatitis B or C infection, you may experience a worsening of your liver problems. Talk to your doctor immediately if you get dark (tea-colored) urine, itching, yellowing of your skin or the white part of your eyes, pain around the stomach, pale-colored stools, or nausea.

- Gallbladder problems uncommonly happen in people taking REYATAZ. Symptoms of gallbladder problems may include pain in the right or middle upper stomach area, nausea, vomiting, fever, or yellowing your skin or the white part of your eyes.
- REYATAZ may affect how well your kidneys work.
- Kidney stones uncommonly happen in people taking REYATAZ. Talk to your doctor immediately if you get symptoms of kidney stones which may include, pain in your low back or low stomach area, blood in your urine, or pain when you urinate.

Other side effects reported for patients treated with REYATAZ are the following:

Common (may affect up to 1 in 10 people):
- headache
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people):
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- angioedema (severe swelling of the skin and other tissues most often the lips or the eyes)
- alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- interstitial nephritis (kidney inflammation), haematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare (may affect up to 1 in 1,000 people):
- gait disturbance (abnormal manner of walking)
- oedema (swelling)
- hepatosplenomegaly (enlargement of the liver and spleen)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store REYATAZ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label, carton, or blister. The expiry date refers to the last day of that month.
Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What REYATAZ contains

- The active substance is atazanavir. Each capsule contains 200 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatin, shellac, ammonium hydroxide, simethicone, propylene glycol, indigocarmin (E132), and titanium dioxide (E171).

What REYATAZ looks like and contents of the pack

Each capsule of REYATAZ 200 mg contains 200 mg atazanavir.
Opaque blue capsule printed with white ink, with "BMS 200 mg" on one half and with "3631" on the other half.

REYATAZ 200 mg hard capsules are supplied in bottles of 60 capsules. Either one or three bottles of 60 hard capsules are provided in one carton.

REYATAZ 200 mg hard capsules are also supplied in blister strips in packs of 60 capsules.

Not all pack sizes may be marketed in all countries.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

REYATAZ 300 mg hard capsules
atazanavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What REYATAZ is and What it is used for

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called *protease inhibitors*. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

REYATAZ capsules may be used by adults and children 6 years of age and older. Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It is normally used in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

2. What you need to know before you take REYATAZ

Do not take REYATAZ
- **if you are allergic** to atazanavir or any of the other ingredients of this medicine (listed in section 6)
- **if you have moderate to severe liver problems.** Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- **if you are taking any of these medicines:** see also *Other medicines and REYATAZ*
  - rifampicin (an antibiotic used to treat tuberculosis)
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches); and alfuzosin (used to treat enlarged prostatic gland)
  - quetiapine (used to treat schizophrenia, bipolar disorder, and major depressive disorder); lurasidone (used to treat schizophrenia)
  - medicines containing St. John's wort *(Hypericum perforatum*, an herbal preparation)

- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety)
- lomitapide, simvastatin, and lovastatin (used to lower blood cholesterol)
- grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination, and glecaprevir/pibrentasvir fixed-dose combination (used to treat chronic hepatitis C infection)
- apalutamide (used to treat prostate cancer), encorafenib (used to treat cancer) and ivosidenib (used to treat cancer)
- carbamazepine, phenobarbital, and phenytoin (used to treat seizures)

Do not take sildenafil with REYATAZ when sildenafil is used for the treatment of pulmonary arterial hypertension. Sildenafil is also used for the treatment of erectile dysfunction. Tell your doctor if you are using sildenafil for the treatment of erectile dysfunction.

Tell your doctor at once if any of these apply to you.

Warnings and precautions

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection.

Some people will need special care before or while taking REYATAZ. Talk to your doctor or pharmacist before taking REYATAZ and make sure your doctor knows:

- if you have hepatitis B or C
- if you develop signs or symptoms of gall stones (pain at the right side of your stomach)
- if you have type A or B haemophilia
- if you require haemodialysis

REYATAZ may affect how well your kidneys work.

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in hands and feet and moving up towards the trunk of the body, palpitations, tremor, or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder), and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

Serious skin rash, including Stevens-Johnson syndrome, has been reported in patients taking REYATAZ. If you develop a rash inform your doctor immediately.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor. Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

Children

Do not give this medicine to children younger than 3 months of age and weighing less than 5 kg. The use of REYATAZ in children less than 3 months of age and weighing less than 5 kg has not been studied due to the risk of serious complications.

Other medicines and REYATAZ

You must not take REYATAZ with certain medicines. These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking, have recently taken, or might take any other medicines. It is especially important to mention these:

- other medicines to treat HIV infection (e.g., indinavir, nevirapine, and efavirenz)
- sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C)
- sildenafil, vardenafil, or tadalafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive (**"the Pill"**) with REYATAZ to prevent pregnancy, be sure to take it exactly as instructed by your doctor and not miss any doses
- any medicines used to treat diseases related to the acid in the stomach (e.g., antacids to be taken 1 hour before taking REYATAZ or 2 hours after taking REYATAZ, H_2-blockers like famotidine and proton pump inhibitors like omeprazole)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm (amiodarone, diltiazem, systemic lidocaine, verapamil)
- atorvastatin, pravastatin, and fluvastatin (used to lower blood cholesterol)
- salmeterol (used to treat asthma)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, clopidogrel, prasugrel, and ticagrelor (used to reduce blood clots)
- lamotrigine (antiepileptic)
- irinotecan (used to treat cancer)
- elagolix (gonadotropin-releasing hormone receptor antagonists, used to treat severe pain from endometriosis)
- fostamatinib (used to treat chronic immune thrombocytopenia)
- sedative agents (e.g. midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain)
- corticosteroids (all routes of administration; including dexamethasone).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking an inhaled or nasal (given in the nose) corticosteroid, including fluticasone or budesonide (given to treat allergic symptoms or asthma).

REYATAZ with food and drink

It is important that you take REYATAZ with food (a meal or a substantial snack) as this helps the body absorb the medicine.

Pregnancy and breast-feeding

If you are pregnant or think that you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Atazanavir, the active substance of REYATAZ, is excreted in human milk. Patients should not breast-feed while taking REYATAZ.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***.

Driving and using machines

If you feel dizzy or lightheaded, do not drive or use machines and contact your doctor immediately.

REYATAZ contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars (e.g., lactose), contact your doctor before taking this medicinal product.

3. How to take REYATAZ

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

The recommended adult dose of REYATAZ capsules is 300 mg once daily with 100 mg ritonavir once daily and with food, in combination with other anti-HIV medicines. Your doctor may adjust the dose of REYATAZ according to your anti-HIV therapy.

For children (6 to less than 18 years of age), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ capsules for children is calculated by body weight and is taken once daily with food and 100 mg ritonavir as shown below:

Body Weight (kg)	**REYATAZ Dose once daily (mg)**	**Ritonavir Dose* once daily (mg)**
15 to less than 35	200	100
at least 35	300	100

*Ritonavir capsules, tablets, or oral solution may be used.

REYATAZ is also available as an oral powder for use in children at least 3 months old and weighing at least 5 kg. Switching to REYATAZ capsules from REYATAZ oral powder is encouraged as soon as patients are able to consistently swallow capsules.

A change in dose may occur when switching between oral powder and capsules. Your doctor will decide the right dose based on your child’s weight.

There are no dosing recommendations for REYATAZ in paediatric patients less than 3 months of age.

Take REYATAZ capsules with food (a meal or a substantial snack). Swallow the capsules whole. **Do not open the capsules.**

If you take more REYATAZ than you should

Yellowing of the skin and/or eyes (jaundice) and irregular heartbeat (QTc prolongation) may occur if you or your child take too much REYATAZ.
If you accidentally take more REYATAZ capsules than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

If you forget to take REYATAZ

If you miss a dose, take the missed dose as soon as possible with food and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at its regular time. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking REYATAZ

Do not stop taking REYATAZ before talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Tell your doctor immediately if you develop any of the following serious side effects:

- Skin rash, itching that may occasionally be severe has been reported. The rash usually disappears within 2 weeks without any change to your REYATAZ treatment. Severe rash may be developed in association with other symptoms which could be serious. Stop taking REYATAZ and talk to your doctor immediately if you develop a severe rash or a rash with flu-like illness symptoms, blisters, fever, mouth sores, muscle or joint pain, swelling in the face, inflammation of the eye which causes redness (conjunctivitis), painful, warm, or red lumps (nodules).
- Yellowing of your skin or the white part of your eyes caused by high levels of bilirubin in your blood has been commonly reported. This side effect is usually not dangerous in adults and infants older than 3 months of age; but it might be a symptom of a serious problem. If your skin or the white part of your eyes turns yellow, talk to your doctor immediately.
- Changes in the way your heart beats (heart rhythm change) may occasionally happen. Talk to your doctor immediately if you get dizzy, lightheaded or if you suddenly faint. These could be symptoms of a serious heart problem.
- Liver problems may uncommonly happen. Your doctor should do blood tests prior you start REYATAZ and during treatment. If you have liver problems, including hepatitis B or C infection, you may experience a worsening of your liver problems. Talk to your doctor immediately if you get dark (tea-colored) urine, itching, yellowing of your skin or the white part of your eyes, pain around the stomach, pale-colored stools, or nausea.

- Gallbladder problems uncommonly happen in people taking REYATAZ. Symptoms of gallbladder problems may include pain in the right or middle upper stomach area, nausea, vomiting, fever, or yellowing your skin or the white part of your eyes.
- REYATAZ may affect how well your kidneys work.
- Kidney stones uncommonly happen in people taking REYATAZ. Talk to your doctor immediately if you get symptoms of kidney stones which may include, pain in your low back or low stomach area, blood in your urine, or pain when you urinate.

Other side effects reported for patients treated with REYATAZ are the following:

Common (may affect up to 1 in 10 people):
- headache
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people):
- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- angioedema (severe swelling of the skin and other tissues most often the lips or the eyes)
- alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- interstitial nephritis (kidney inflammation), haematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare (may affect up to 1 in 1,000 people):
- gait disturbance (abnormal manner of walking)
- oedema (swelling)
- hepatosplenomegaly (enlargement of the liver and spleen)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store REYATAZ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label, carton, or blister. The expiry date refers to the last day of that month.
Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What REYATAZ contains

- The active substance is atazanavir. Each capsule contains 300 mg of atazanavir (as sulphate).
- The other ingredients are crospovidone, lactose monohydrate, and magnesium stearate. The capsule shell and printing ink contain gelatin, shellac, ammonium hydroxide, simethicone, red iron oxide, black iron oxide, yellow iron oxide, propylene glycol, indigocarmin (E132), and titanium dioxide (E171).

What REYATAZ looks like and contents of the pack

Each capsule of REYATAZ 300 mg contains 300 mg atazanavir.
Opaque red and blue capsule printed with white ink, with "BMS 300 mg" on one half and with "3622" on the other half.

REYATAZ 300 mg hard capsules are supplied in bottles of 30 capsules. Either one or three bottles of 30 hard capsules are provided in one carton.

REYATAZ 300 mg hard capsules are also supplied in blister strips in packs of 30 capsules.

Not all pack sizes may be marketed in all countries.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

CATALENT ANAGNI S.R.L.
Loc. Fontana del Ceraso snc
Strada Provinciale 12 Casilina, 41
03012 Anagni (FR)
Italy

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations, External Manufacturing
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

REYATAZ 50 mg oral powder
atazanavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

1. What REYATAZ is and What it is used for

REYATAZ is an antiviral (or antiretroviral) medicine. It is one of a group called *protease inhibitors*. These medicines control Human Immunodeficiency Virus (HIV) infection by stopping a protein that the HIV needs for its multiplication. They work by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way REYATAZ reduces the risk of developing illnesses linked to HIV infection.

REYATAZ oral powder may be used by children at least 3 months of age and weighing at least 5 kg (see section 3 How to take REYATAZ). Your doctor has prescribed REYATAZ for you because you are infected by the HIV that causes Acquired Immunodeficiency Syndrome (AIDS). It should always be used with a low dose of ritonavir and in combination with other anti-HIV medicines. Your doctor will discuss with you which combination of these medicines with REYATAZ is best for you.

2. What you need to know before you take REYATAZ

Do not take REYATAZ

- **if you are allergic** to atazanavir or any of the other ingredients of this medicine (listed in section 6)
- **if you have moderate to severe liver problems.** Your doctor will evaluate how severe your liver disease is before deciding whether you can take REYATAZ
- **if you are taking any of these medicines:** see also *Other medicines and REYATAZ*
  - rifampicin (an antibiotic used to treat tuberculosis)
  - astemizole or terfenadine (commonly used to treat allergy symptoms, these medicines may be available without prescription); cisapride (used to treat gastric reflux, sometimes called heartburn); pimozide (used to treat schizophrenia); quinidine or bepridil (used to correct heart rhythm); ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches); and alfuzosin (used to treat enlarged prostatic gland)
  - quetiapine (used to treat schizophrenia, bipolar disorder, and major depressive disorder); lurasidone (used to treat schizophrenia)
  - medicines containing St. John's wort *(Hypericum perforatum*, an herbal preparation)

- triazolam and oral (taken by mouth) midazolam (used to help you sleep and/or to relieve anxiety)
- lomitapide, simvastatin, and lovastatin (used to lower blood cholesterol).
- grazoprevir-containing products, including elbasvir/grazoprevir fixed-dose combination, and glecaprevir/pibrentasvir fixed-dose combination (used to treat chronic hepatitis C infection)
- apalutamide (used to treat prostate cancer), encorafenib (used to treat cancer), ivosidenib (used to treat cancer)
- carbamazepine, phenobarbital, and phenytoin (used to treat seizures)

Do not take sildenafil with REYATAZ when sildenafil is used for the treatment of pulmonary arterial hypertension. Sildenafil is also used for the treatment of erectile dysfunction. Tell your doctor if you are using sildenafil for the treatment of erectile dysfunction.

Tell your doctor at once if any of these apply to you.

Warnings and precautions

REYATAZ is not a cure for HIV infection. You may continue to develop infections or other illnesses linked to HIV infection.

Some people will need special care before or while taking REYATAZ. Talk to your doctor or pharmacist before taking REYATAZ and make sure your doctor knows:

- if you have hepatitis B or C
- if you develop signs or symptoms of gall stones (pain at the right side of your stomach)
- if you have type A or B haemophilia
- if you require haemodialysis

REYATAZ may affect how well your kidneys work.

Kidney stones have been reported in patients taking REYATAZ. If you develop signs or symptoms of kidney stones (pain in your side, blood in your urine, pain when you urinate), please inform your doctor immediately.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in hands and feet and moving up towards the trunk of the body, palpitations, tremor, or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder), and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Hyperbilirubinaemia (an increase in the level of bilirubin in the blood) has occurred in patients receiving REYATAZ. The signs may be a mild yellowing of the skin or eyes. If you notice any of these symptoms please inform your doctor.

Serious skin rash, including Stevens-Johnson syndrome, has been reported in patients taking REYATAZ. If you develop a rash inform your doctor immediately.

If you notice a change in the way your heart beats (heart rhythm changes), please inform your doctor. Children receiving REYATAZ may require their heart to be monitored. Your child's doctor will decide this.

Children

Do not give this medicine to children younger than 3 months of age and weighing less than 5 kg. The use of REYATAZ in children less than 3 months of age and weighing less than 5 kg has not been studied due to the risk of serious complications.

Other medicines and REYATAZ

You must not take REYATAZ with certain medicines. These are listed under Do not take REYATAZ, at the start of Section 2.

There are other medicines that may not mix with REYATAZ. Tell your doctor if you are taking, have recently taken, or might take any other medicines. It is especially important to mention these:

- other medicines to treat HIV infection (e.g., indinavir, nevirapine, and efavirenz)
- sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C)
- sildenafil, vardenafil, or tadalafil (used by men to treat impotence (erectile dysfunction))
- if you are taking an oral contraceptive (**"the Pill"**) with REYATAZ to prevent pregnancy, be sure to take it exactly as instructed by your doctor and not miss any doses
- any medicines used to treat diseases related to the acid in the stomach (e.g., antacids to be taken 1 hour before taking REYATAZ or 2 hours after taking REYATAZ, H_2-blockers like famotidine and proton pump inhibitors like omeprazole)
- medicines to lower blood pressure, to slow heart rate, or to correct heart rhythm (amiodarone, diltiazem, systemic lidocaine, verapamil)
- atorvastatin, pravastatin, and fluvastatin (used to lower blood cholesterol)
- salmeterol (used to treat asthma)
- cyclosporin, tacrolimus, and sirolimus (medicines to decrease the effects of body's immune system)
- certain antibiotics (rifabutin, clarithromycin)
- ketoconazole, itraconazole, and voriconazole (antifungals)
- apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, clopidogrel, prasugrel, and ticagrelor (used to reduce blood clots)
- lamotrigine (antiepileptic)
- irinotecan (used to treat cancer)
- elagolix (gonadotropin-releasing hormone receptor antagonists, used to treat severe pain from endometriosis)
- fostamatinib (used to treat chronic immune thrombocytopenia)
- sedative agents (e.g., midazolam administered by injection)
- buprenorphine (used to treat opioid addiction and pain)
- corticosteroids (all routes of administration; including dexamethasone).

Some medicines may interact with ritonavir, a medicine that is taken with REYATAZ. It is important to tell your doctor if you are taking an inhaled or nasal (given in the nose) corticosteroid, including fluticasone or budesonide (given to treat allergic symptoms or asthma).

REYATAZ with food and drink

See section 3 How to take REYATAZ.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Atazanavir, the active substance of REYATAZ, is excreted in human milk. Patients should not breast-feed while taking REYATAZ.

Breast-feeding ***is not recommended*** in women who living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***.

Driving and using machines

If you feel dizzy or lightheaded, do not drive or use machines, and contact your doctor immediately.

REYATAZ oral powder contains:

- 63 mg of aspartame per sachet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
- 1.3 g of sucrose per sachet. This should be taken into account in patients with diabetes mellitus. May be harmful to the teeth. If you have been told by your doctor that your child has an intolerance to some sugars, contact your doctor before giving this medicinal product to your child.

3. How to take REYATAZ

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This way, you can be sure your medicine is fully effective and you reduce the risk of the virus developing resistance to the treatment.

For children (at least 3 months of age and weighing at least 5 kg), your child's doctor will decide the right dose based on your child's weight. The dose of REYATAZ oral powder for children is calculated by body weight and is taken once daily with food and ritonavir as shown below:

Body Weight (kg)	**REYATAZ Dose once daily (mg)**	**Ritonavir Dose once daily (mg)**
At least 5 to less than 15	200 mg (4 sachets[a])	80 mg[b]
At least 15 to less than 35	250 mg (5 sachets[a])	80 mg[b]
at least 35	300 mg (6 sachets[a])	100 mg[c]

[a] Each sachet contains 50 mg of REYATAZ
[b] Ritonavir oral solution
[c] Ritonavir oral solution or capsule/tablet

REYATAZ is also available in capsules for use in adults and children at least 6 years of age who weigh at least 15 kg and who are able to swallow the capsules. Switching from REYATAZ oral powder to REYATAZ capsules is encouraged as soon as patients are able to consistently swallow capsules.

A change in dose may occur when switching between oral powder and capsules. Your doctor will decide the right dose based on your child's weight.

There are no dosing recommendations for REYATAZ in paediatric patients less than 3 months of age.

Instructions for REYATAZ oral powder:

- For children who are able to drink from a cup, REYATAZ oral powder must be taken with food or drinks. If REYATAZ oral powder is mixed with water, food should also be taken at the same time.
- For children who cannot eat solid food or drink from a cup, REYATAZ oral powder must be mixed with infant formula and should be given using an oral syringe. Ask your pharmacist for an oral syringe. Do not use an infant bottle to give REYATAZ mixed with infant formula.
- See the "Instructions for use" at the end of the package leaflet for how to prepare and give a dose of REYATAZ oral powder.
- REYATAZ oral powder should be given within 60 minutes of mixing.

If you take more REYATAZ than you should

Yellowing of the skin and/or eyes (jaundice) and irregular heart beat (QTc prolongation) may occur if you or your child take too much REYATAZ.
If you accidentally take or give more REYATAZ oral powder than your doctor recommended, contact your HIV doctor at once or contact the nearest hospital for advice.

If you forget to take REYATAZ

If you miss a dose or if you forget to give your child a dose, take or give the missed dose as soon as possible with food and then take or give the next scheduled dose at its regular time. If it is almost time for your or your child's next dose, do not take or give the missed dose. Wait and take or give the next dose at its regular time. **Do not take or give a double dose to make up for a forgotten dose.**

If you stop taking REYATAZ

Do not stop taking REYATAZ before talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always easy to identify what side effects are caused by REYATAZ, by the other medicines you are taking, or by the HIV infection itself. Tell your doctor if you notice anything unusual about your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Tell your doctor immediately if you develop any of the following serious side effects:

- Skin rash, itching that may occasionally be severe has been reported. The rash usually disappears within 2 weeks without any change to your REYATAZ treatment. Severe rash may be developed in association with other symptoms which could be serious. Stop taking REYATAZ and talk to your doctor immediately if you develop a severe rash or a rash with flu-like illness symptoms, blisters, fever, mouth sores, muscle or joint pain, swelling in the face,

inflammation of the eye which causes redness (conjunctivitis), painful, warm, or red lumps (nodules).

- Yellowing of your skin or the white part of your eyes caused by high levels of bilirubin in your blood has been commonly reported. This side effect is usually not dangerous in adults and infants older than 3 months of age; but it might be a symptom of a serious problem. If your skin or the white part of your eyes turns yellow, talk to your doctor immediately.
- Changes in the way your heart beats (heart rhythm change) may occasionally happen. Talk to your doctor immediately if you get dizzy, lightheaded or if you suddenly faint. These could be symptoms of a serious heart problem.
- Liver problems may uncommonly happen. Your doctor should do blood tests prior you start REYATAZ and during treatment. If you have liver problems, including hepatitis B or C infection, you may experience a worsening of your liver problems. Talk to your doctor immediately if you get dark (tea-colored) urine, itching, yellowing of your skin or the white part of your eyes, pain around the stomach, pale-colored stools, or nausea.
- Gallbladder problems uncommonly happen in people taking REYATAZ. Symptoms of gallbladder problems may include pain in the right or middle upper stomach area, nausea, vomiting, fever, or yellowing your skin or the white part of your eyes.
- REYATAZ may affect how well your kidneys work.
- Kidney stones uncommonly happen in people taking REYATAZ. Talk to your doctor immediately if you get symptoms of kidney stones which may include, pain in your low back or low stomach area, blood in your urine, or pain when you urinate.

Other side effects reported for patients treated with REYATAZ are the following:

Common (may affect up to 1 in 10 people):

- headache
- vomiting, diarrhoea, abdominal pain (stomach pain of discomfort), nausea, dyspepsia (indigestion)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people):

- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- hypersensitivity (allergic reaction)
- asthenia (unusual tiredness or weakness)
- weight decreased, weight gain, anorexia (loss of appetite), appetite increased
- depression, anxiety, sleep disorder
- disorientation, amnesia (loss of memory), dizziness, somnolence (sleepiness), abnormal dream
- syncope (fainting), hypertension (high blood pressure)
- dyspnoea (shortness of breath)
- pancreatitis (inflammation of the pancreas), gastritis (inflammation of the stomach), stomatitis aphthous (mouth ulcers and cold sores), dysgeusia (impairment of the sense of taste), flatulence (wind), dry mouth, abdominal distension
- angioedema (severe swelling of the skin and other tissues most often the lips or the eyes)
- alopecia (unusual hair loss or thinning), pruritus (itching)
- muscle atrophy (muscle shrinkage), arthralgia (joint pain), myalgia (aching muscles)
- interstitial nephritis (kidney inflammation), haematuria (blood in the urine), proteinuria (excess protein in the urine), pollakiuria (increased frequency of urination)
- gynaecomastia (breast enlargement in men)
- chest pain, malaise (generally feeling unwell), fever
- insomnia (difficulty sleeping)

Rare (may affect up to 1 in 1,000 people):

- gait disturbance (abnormal manner of walking)
- oedema (swelling)
- hepatosplenomegaly (enlargement of the liver and spleen)
- myopathy (aching muscles, muscle tenderness of weakness, not caused by exercise)
- kidney pain

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store REYATAZ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or sachet. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions. Do not open the sachet until ready to use.

After mixing the oral powder with food or drinks, it may be stored at room temperature (not above 30°C) for up to 1 hour.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What REYATAZ contains

- The active substance is atazanavir. Each sachet contains 50 mg of atazanavir (as sulphate).
- The other ingredients are aspartame (E951), sucrose, and orange vanilla flavour.

What REYATAZ looks like and contents of the pack

Each sachet of REYATAZ 50 mg oral powder contains 50 mg atazanavir.

One pack size is available: 1 carton with 30 sachets.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

Swords Laboratories Unlimited Company T/A Lawrence Laboratories
Unit 12 & 15, Distribution Centre
Shannon Industrial Estate
Shannon, Co. Clare, V14 DD39
Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Instructions for use

These instructions show you how to prepare and give a dose of REYATAZ oral powder. Make sure that you read and understand these instructions before giving this medicine to your child.
Your child's doctor will decide the right dose based on your child's age and weight.

Always give your child the medicine within 60 minutes of mixing.

Before giving the medicine

1. Determine the dose and the number of REYATAZ oral powder sachets needed (see section 3 How to take REYATAZ).
2. Before use, tap the sachet. Cut each sachet along the dotted line.
3. Choose the appropriate option listed below for giving REYATAZ oral powder to your child. Larger volumes or quantities of liquid infant formula, beverage or food may be used. Ensure that all the infant formula, beverage or food that contains the medicine is taken.

Preparing and giving the medicine with liquid infant formula using a medicine cup or small container and oral syringe (ask your pharmacist for an oral syringe**):**

1. Take a medicine cup or small container and put the sachets' content in the cup or small container.
2. Add 10 mL of prepared liquid infant formula and mix using a spoon.
3. Put the oral syringe tip into the mixture and pull back the plunger until the full amount of infant formula is taken up.
4. Place the syringe in your child's mouth towards the cheek and push the plunger down to release the medicine.
5. Put another 10 mL of prepared infant formula in the cup or container and rinse the remaining oral powder from the cup or container.
6. Put the syringe tip into the mixture and pull back the plunger until the full amount of infant formula is taken up.
7. Place the syringe in your child's mouth towards the cheek and push the plunger down to release the medicine.
8. Give to your child the recommended dose of ritonavir immediately after giving REYATAZ oral powder.

Preparing and giving the medicine with drinks

1. Put the sachets' content in a small drinking cup.
2. Add 30 mL of the drink and mix with a spoon.
3. Have the child drink the mixture.
4. Add another 15 mL of the drink, mix, and have the child drink the mixture.
5. If water is used, food should also be taken at the same time.

Preparing and giving the medicine with food

1. Fill a small container with the sachets' content.
2. Add a minimum of one tablespoon of food and mix.
3. Feed your child with the mixture.
4. Add an additional tablespoon in the container, mix and feed to your child again.

If you have any questions on how to prepare or give a dose of REYATAZ oral powder, talk to your doctor, pharmacist or nurse.