1.6 Product Information

1.6.1 Prescribing information (Summary of products characteristics)

Summary of Product Characteristics (SmPC) is enclosed overleaf.

ANZAVIR – R
Atazanavir (as sulfate) / Ritonavir Tablets
300 mg / 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Atazanavir (as sulfate) equivalent to Atazanavir	300 mg
Ritonavir USP	100 mg

Excipients with known effect: lactose, sorbitol and sodium.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Bilayered, capsule shaped, biconvex, film-coated tablet having one layer plain with pale yellow to yellow colour and a white to off-white layer debossed with “M777”.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is indicated for the treatment of HIV-1 infected adults and children weighing at least 39 kg, in combination with other antiretroviral medicinal products.

The choice of Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see Special warnings and precautions for use and Pharmacodynamic properties).

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

4.2 Posology and method of administration

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should be prescribed by physicians who are experienced in the treatment of HIV infection.

In patients weighing ≥ 39 kg, the recommended dose is one tablet given once daily, in combination with other antiretroviral agents.

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets must be taken with food.

***Hepatic impairment*:** Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should be used with caution in patients with mild hepatic impairment. Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is contraindicated in patients with moderate to severe hepatic impairment (see Contraindications, Special warnings and precautions for use, and Pharmacokinetic properties).

***Renal impairment*:** No dosage adjustment is needed. Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is not recommended in patients undergoing haemodialysis (see Special warnings and precautions for use and Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients (see List of Excipients).

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets must not be administered to patients with decompensated liver disease (see Posology and method of administration and Special warnings and precautions for use)

Ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated drug metabolism. Furthermore, atazanavir and ritonavir are themselves substrates for CYP3A. The following medicines are contraindicated when Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is used due to the risk of adverse effects or loss of efficacy due to drug-drug interactions (see also Special warnings and precautions for use and Interactions with other medicinal products and other forms of interaction).

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased		
α_1-Adrenoreceptor Antagonists	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension.
Analgesics	Pethidine, propoxyphene	Increased plasma concentrations of norpethidine, and propoxyphene, thereby, increasing the risk of serious respiratory depression or other serious adverse effects from these agents.
Antiarrhythmics	Amiodarone, Bepridil, Encainide, Flecainide, Propafenone, Quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotics	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antimalarials	Halofantrine	Increased plasma concentration of halofantrine may increase the risk of severe cardiac arrhythmias.
Antihistamines	Astemizole, Terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/ Neuroleptics	Pimozide	Increased plasma concentrations of pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.

Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
Concomitant medicinal product levels increased		
GI motility agents	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.
HMG Co-A Reductase Inhibitors	Lovastatin, Simvastatin	Increased plasma concentrations of lovastatin and simvastatin. Thereby, increasing the risk of myopathy including rhabdomyolysis (see Special warnings and precautions for use and Interactions with other medicinal products and other forms of interaction).
PDE5 inhibitors	Sildenafil, Vardenafil	Vardenafil is contraindicated for all co-treatment with Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets. Sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil and vardenafil are expected. Thereby, increasing the potential for sildenafil- or vardenafil associated adverse events (which include hypotension and syncope). See Special warnings and precautions for use and Interactions with other medicinal products and other forms of interaction for coadministration of sildenafil in patients with erectile dysfunction.
Sedatives/hypnotics	Clorazepate, Diazepam, Estazolam, Flurazepam, oral Midazolam and Triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterally administered midazolam, see Interactions with other medicinal products and other forms of interaction)
Atazanavir/ ritonavir medicinal product level decreased		
Antimycobacterials	Rifampicin	Decreased plasma concentration and reduced clinical effect of atazanavir and ritonavir (see also Interactions with other medicinal products and other forms of interaction.)
Herbal Preparations	St. John's Wort	Decreased plasma concentrations and reduced clinical effects of atazanavir/ritonavir

4.4 Special warnings and precautions for use

Transmission of HIV: Antiretroviral therapy has not been proven to eliminate the risk of transmission of HIV to others through sexual contact or contamination with blood. Patients should continue to take appropriate precautions.

Opportunistic infections: Patients taking Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets may still develop infections or other illnesses associated with HIV infection and AIDS.

Hepatic impairment**:** Atazanavir is primarily hepatically metabolised and increased plasma concentrations have been observed in patients with hepatic impairment (see Posology and method of administration and Contraindications). The safety and efficacy of Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets has not been established in patients with significant underlying liver disorders. Patients with pre-existing liver dysfunction, including chronic hepatitis B or C, that are treated with combination antiretroviral therapy, are at an increased risk for severe and potentially fatal hepatic adverse reactions. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered. 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.

Renal impairment: No dosage adjustment is needed in patients with renal impairment. However, Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is not recommended in patients undergoing haemodialysis.

Haemophilia: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses in patients with haemophilia type A and B treated with protease inhibitors. 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.

Hyperlipidaemia**:** Combination antiretroviral therapy, including atazanavir/ritonavir-based regimens, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see Undesirable effects).

In clinical studies, atazanavir (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk.

Hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these cases hyperglycaemia was severe and also associated with ketoacidosis. Many patients had confounding medical conditions. A causal relation between atazanavir with ritonavir and these events has not been established.

Lipodystrophy: Combination antiretroviral therapy has been associated with changes in the distribution of body fat (lipodystrophy) in HIV patients. A higher risk of peripheral fat loss has been associated with stavudine or zidovudine use, and also with individual factors such as older age of the patient, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for changes in body shape.

Hyperbilirubinaemia: Reversible elevations in indirect (unconjugated) bilirubin, related to inhibition of UDP-glucuronosyl transferase (UGT), have occurred in patients receiving atazanavir (see Undesirable effects). Hepatic transaminase elevations that occur with elevated bilirubin in patients

receiving atazanavir should be evaluated for alternative aetiologies. Alternative antiretroviral therapy to Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should 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.

Nephrolithiasis: Nephrolithiasis has been reported in patients receiving atazanavir (see Undesirable effects). If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment with Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets may be considered.

PR interval prolongation**:** Dose related asymptomatic prolongations in PR interval with atazanavir have been observed in clinical studies. Caution should be used when co-administering with medicinal products known to induce PR prolongation. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle branch block), Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should be used with caution and only if the benefits exceed the risk (see Pharmacodynamic properties).

Particular caution should be used when prescribing Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets together with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors e.g. bradycardia, congenital long QT-syndrome, electrolyte imbalances (see Undesirable effects and Preclinical safety data).

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of commencing combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions occur within the first few weeks or months after treatment initiation. Examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), 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 Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets. 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 Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should be discontinued if severe rash develops.

Early diagnosis and immediate interruption of any suspect medicines are important in the management of such events. If the patient has developed SJS or DRESS associated with the use of Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets, Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets should be permanently discontinued.

Interactions with other medicinal products

Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets is a co-formulation of atazanavir and ritonavir. The latter is a very strong inhibitor of CYP3A and an inducer of hepatic drug metabolising enzymes. Atazanavir is metabolised principally by CYP3A and drug levels may be reduced when co-administering

CYP3A inducers. For these reasons Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets may interact with a number of other medicinal products, leading to loss of efficacy or toxicity of either agent.

For contraindicated co-prescribing, see Contraindications. Further combinations which should be avoided include, but are not limited to, NNRTIs, hormonal contraceptives, some HMG-CoA reductase inhibitors and some corticosteroids (see Interactions with other medicinal products and other forms of interaction) Furthermore, the bioavailablity of atazanavir is pH dependent, and absorption is reduced in situations where gastric pH is increased irrespective of cause. Therefore, co-administration of Atazanavir (as sulfate)/Ritonavir 300mg/100mg Tablets and proton pump inhibitors is not recommended (see Interactions with other medicinal products and other forms of interaction).

Excipients
Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets contains a small amount of lactose and sorbitol. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

4.5 Interactions with other medicinal products and other forms of interaction
Atazanavir is metabolised in the liver through cytochrome P450 (CYP) 3A4, which it inhibits. Ritonavir has a high affinity for several CYP isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For select medicinal products (e.g. alprazolam) the inhibitory effects of ritonavir on CYP3A4 may decrease over time. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time (e.g. digoxin and fexofenadine - see table “Ritonavir effects on non-antiretroviral medicinal products” below). Ritonavir may also induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect. When atazanavir and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: examples include but are not limited to astemizole, terfenadine, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids (see Contraindications).

Co-treatments that require special considerations include, but are not limited, to the following:

NNRTIs: Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with nevirapine or efavirenz is not recommended (see also below). If co-administration of atazanavir and ritonavir with an NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered, along with close clinical monitoring. This dose adjustment cannot be achieved with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.[*]

[*] This dose of atazanavir and ritonavir cannot be achieved with this formulation.
[r.]This dose of atazanavir cannot be achieved with this formulation.

Rifampicin: Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with rifampicin is contraindicated. Rifampicin in combination with atazanavir and ritonavir causes large decreases in atazanavir concentrations which may lead to decreased therapeutic effect of atazanavir and development of resistance. Use of higher doses of atazanavir or other protease inhibitors in attempts to achieve satisfactory exposure has resulted in a high frequency of hepatotoxicity.

HMG-CoA reductase inhibitors**:** Simvastatin and lovastatin are highly dependent on CYP3A for metabolism; thus concomitant use of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised with rosuvastatin or atorvastatin, which are metabolised to a lesser extent by CYP3A4, and reduced doses of these agents should be considered if they are co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin are primarily recommended (see table below).

CYP3A4 inducers: Atazanavir is metabolised principally by CYP3A4. Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and medicinal products that induce CYP3A4 is not recommended (see Contraindications and table below).

Antifungals**:** Co-administration of voriconazole and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole (see table below).

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

Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with proton pump inhibitors is not recommended (see table below). If the combination of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended, combined with an increase in the dose of atazanavir 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 Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets in combination with tenofovir and an H_2-receptor antagonist should be avoided (see table below).

Hormonal contraceptives**:** If an oral contraceptive is administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, it is recommended that the oral contraceptive contains at least 30 µg of ethinylestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternative reliable method of contraception is recommended.

Glucocorticoids**:** Concomitant use of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with 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 Interactions with other medicinal products and other forms of interaction).

Interaction list**:** Interactions between atazanavir/ritonavir or ritonavir only and selected co-administered medicinal products are listed in the table below; the studies presented in Table 1 were

conducted in healthy adult subjects unless otherwise noted. Significantly, some studies were conducted with atazanavir without ritonavir, i.e. unboosted. Also, in some cases, interaction data pertain to ritonavir only.

Table 1: Interactions between Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and other medicinal products

Co-administered medicinal product	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Didanosine (buffered tablets) 200 mg / Stavudine 40 mg, both single dose (Atazanavir 400 mg single dose)	Atazanavir (simultaneous dosing with ddI+d4T, fasted) AUC ↓ 87%, C_{min} ↓ 84% Atazanavir (dosed 1 hr. after ddI+d4T, fasted) AUC ↑ 3%, C_{min} ↑ 3%, The mechanism of interaction is reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets.	Didanosine should be taken in the fasted state 2 hours after Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets taken with food. The co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and ritonavir with stavudine is not expected to significantly alter the exposure of stavudine. Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. No significant effect on didanosine and stavudine concentrations was observed.
Didanosine (enteric coated capsules) 400 mg single dose /Atazanavir 300 mg QD with ritonavir 100 mg QD)	Didanosine (with food) AUC ↓ 34%, C_{min} ↑ 25%	No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreases didanosine exposure.
Lamivudine 150 mg BID + Zidovudine 300 mg BID / Atazanavir 400 mg QD	No significant effect on lamivudine or zidovudine concentrations was observed.	No dose adjustment necessary.
Tenofovir disoproxil fumarate 300 mg QD / Atazanavir 300 mg QD with ritonavir 100 mg QD (combined analysis, HIV-infected patients)	Atazanavir AUC ↓ 22%, C_{min} ↓ 23% Tenofovir AUC ↑ 37% C_{min} ↑ 29% The mechanism of interaction between atazanavir and tenofovir is unknown.	The efficacy of atazanavir and ritonavir in combination with tenofovir in treatment-naïve and treatment-experienced patients has been demonstrated in clinical studies (see Undesirable effects and Pharmacodynamic properties). Patients should be closely monitored for tenofovir-associated adverse events, including renal disorders.
Abacavir	Not studied, but no significant interaction is expected.	No dose adjustment recommended.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg QD / Atazanavir 400 mg QD with ritonavir 100 mg QD) Efavirenz 600 mg QD / Atazanavir 400 mg QD with	Atazanavir AUC ↔ C_{min} ↓ 42%, Atazanavir AUC ↑ 6%	Co-administration of efavirenz with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended (see Special warnings and precautions for use).

ritonavir 200 mg QD (all atazanavir pm, administered with food)	C_{min} ↑ 12% (When compared to atazanavir 300 mg /ritonavir 100 mg once daily in the evening without efavirenz. Based on historical comparison)	If co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with an NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered, along with close clinical monitoring.[†*]
Nevirapine 200 mg BID / Atazanavir 400 mg QD with Ritonavir 100 mg QD. Study conducted in HIV infected patients.	Atazanavir AUC ↓ 19%, C_{min} ↓ 59% Nevirapine AUC ↑ 26%, C_{min} ↑ 35%	Co-administration of nevirapine with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended (see Special warnings and precautions for use)
Integrase Inhibitors		
Raltegravir 400 mg BID (Atazanavir/Ritonavir)	Raltegravir AUC ↑ 41%, C_{12hr} ↑↑ 77%	No dose adjustment required for raltegravir.
CCR5 inhibitors		
Maraviroc / (Atazanavir 300 mg/ritonavir 100 mg)	Maraviroc AUC_{12} ↑ 388% Maraviroc C_{max}: ↑ 167% Atazanavir/Ritonavir concentrations not measured, no effect is expected.	Maraviroc dose should be decreased to 150 mg twice daily when co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets. For further information, refer to the Summary of Product Characteristics for Celsentri.
Protease inhibitors: The co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with other protease inhibitors would be expected to increase exposure to other protease inhibitors. Furthermore, no virological benefit of combining two protease inhibitors has been demonstrated. Therefore, such co-administration is not recommended.		
Anti-Mycobacterial		
Rifampicin / Atazanavir	Atazanavir AUC ↓ 72% During attempts to overcome the decreased exposure by increasing the dose of atazanavir or other protease inhibitors with ritonavir, a high frequency of hepatotoxicity was seen.	The combination of rifampicin and atazanavir with concomitant low-dose ritonavir is contraindicated (see Contraindications).
Rifabutin 150 mg twice weekly / Atazanavir 300 mg and ritonavir 100 mg QD)	Rifabutin AUC ↑ 48% C_{min} ↑ 40% 25-O-deacetyl-rifabutin (active metabolite) AUC ↑ 10.9 fold	In adults rifabutin dose should be reduced to 150 mg every other day, or 150 mg thrice weekly, and safety should be closely monitored (e.g. for neutropenia and uveitis).

[*] This dose of atazanavir cannot be achieved with this formulation.

	(compared to rifabutin 150 mg QD alone) In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.	No dose adjustment is necessary for Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Other Anti-infectives		
Antibiotics		
Clarithromycin 500 mg BID / Atazanavir 400 mg QD	Clarithromycin AUC ↑ 94% C_{min} ↑160% 14-OH-clarithromycin (active metabolite) AUC ↓ 70% C_{min} ↓ 62% Atazanavir AUC ↑28%, C_{min} ↑91%	As dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin, the active metabolite, no recommendation regarding dose reduction can be made. Therefore, caution should be exercised if Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is co-administered with clarithromycin.
Erythromycin	Not studied. An increase the plasma concentrations of erythromycin is expected due to inhibition of CYP3A4.	Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is used concomitantly with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Sulfamethoxazole / Trimethoprim		No interaction expected.
Fusidic acid	Not studied. Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir.	Concomitant use of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and fusidic acid is therefore **contraindicated** (see Contraindications).
Antifungals		
Ketoconazole 200 mg QD / Atazanavir 400 mg QD Itraconazole	No significant effect on atazanavir concentrations was observed. Itraconazole, like ketoconazole, is a potent 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, atazanavir with ritonavir is expected to increase ketoconazole or itraconazole concentrations.	Ketoconazole and itraconazole should be used cautiously with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets. High doses of ketoconazole and itraconazole (>200 mg/day) are not recommended.

Vorizonazole	Co-administration of Atazanavir with ritonavir and voriconazole has not been studied. Co-administration of voriconazole and low dose (100 mg) ritonavir in healthy volunteers decreased the AUC and C_{max} of voriconazole by 39% and 24%, respectively. Ritonavir AUC and C_{max} were decreased by 14% and 24%, respectively.	Co-administration of voriconazole and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Patients should be carefully monitored for adverse events and/or loss of efficacy during co-administration of voriconazole and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Fluconazole 200 mg QD / Atazanavir 300 mg and Ritonavir 100 mg QD	Atazanavir and fluconazole concentrations were not significantly modified when atazanavir and ritonavir were co-administered with fluconazole. Other studies have indicated no relevant effect on ritonavir exposure.	No dosage adjustments are needed for Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and fluconazole.
Antimalarials		
Atovaquone + Proguanil	Not studied.	Atovaquone and proguanil exposure may decrease. The therapeutic effect should be carefully monitored.
Artemisinin derivatives	Not studied. CYP3A4 does not appear to play a significant role in metabolism of the artemisinins.	No dose adjustment is considered necessary.
Halofantrine	Not studied	Halofantrine prolongs the QT interval and is metabolized by CYP3A. Co-administration with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is contraindicated. (see Contraindications).
Lumefantrine	Not studied	Lumefantrine is metabolized by CYP3A4 and causes QT prolongation. Lumefantrine and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets should be co-administered with caution.
Quinine	Not studied	Since quinine prolongs the QT-interval and is metabolized by CYP3A, co-administration with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets should be avoided unless the benefit is considered to outweigh the risk.
Chloroquine	Not studied.	Administer with caution and monitor for chloroquine toxicity.

	Chloroquine is metabolised by CYP3A, therefore levels may be increased.	
Mefloquine	Coadministration of ritonavir (200 mg) with mefloquine resulted in no change in mefloquine concentrations and a 31% decrease in ritonavir AUC.	No dose adjustment necessary.
Sulfadoxine + Pyrimethamine	Not studied, but no interaction expected.	No dose adjustment necessary.
Doxycycline	Not studied, but no interaction expected.	No dose adjustment necessary.
ACID REDUCING AGENTS		
H_2-Receptor antagonists		
Without Tenofovir		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg QD		**For patients not taking tenofovir**, if Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and H2-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg BID should not be exceeded. If a higher dose of an H_2-receptor antagonist is required, an increase of atazanavir /ritonavir dose from 300/100 mg to 400/100 mg can be considered.*
Famotidine 20 mg BID	Atazanavir AUC ↓ 18% C_{min} ↓ 1%	
Famotidine 40 mg BID	Atazanavir AUC ↓ 23% C_{min} ↓ 20%	
In healthy volunteers with Atazanavir/Ritonavir at an increased dose of 400/100 mg QD		
Famotidine 40 mg BID	Atazanavir AUC ↑ 3% C_{min} ↓ 24%	

* This dose of atazanavir cannot be achieved with this formulation.

With Tenofovir 300 mg QD		
In HIV-infected patients with Atazanavir/Ritonavir at the recommended dose of 300/100 mg QD		
Famotidine 20 mg BID Famotidine 40 mg BID	Atazanavir AUC ↓ 21%† C_{min} ↓ 19%† Atazanavir AUC ↓ 24%† C_{min} ↓ 25%†	**For patients who are taking tenofovir,** co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets in combination with tenofovir and an H_2-receptor antagonist should be avoided (see Special warnings and precautions for use). If the combination of atazanavir /ritonavir with both tenofovir and an H_2-receptor antagonist is judged unavoidable, close clinical monitoring is recommended; an increase of atazanavir /ritonavir dose from 300/100 mg to 400/100 mg can be considered*
† When compared to atazanavir 300 mg QD with ritonavir 100 mg QD 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, atazanavir concentrations are expected to be additionally decreased by about 20%. The mechanism of interaction is decreased solubility of atazanavir as gastric pH increases with H_2 blockers.		
Proton pump inhibitors		
Omeprazole 40 mg QD / Atazanavir 400 mg QD with Ritonavir 100 mg QD Atazanavir (am): 2 hr after omeprazole Omeprazole 20 mg QD / Atazanavir 400 mg QD with Ritonavir 100 mg QD Atazanavir (am): 1 hr after omeprazole	Atazanavir AUC ↓ 61% C_{min} ↓ 65% Atazanavir AUC ↓ 30% C_{min} ↓ 31%	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with proton pump inhibitors is not recommended. If the combination of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir*; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.
The decrease in atazanavir AUC, C_{max}, and C_{min} was not mitigated when an increased dose of atazanavir and ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Similar results are expected with other proton pump inhibitors.		
Antacids	Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with Atazanavir (as	Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.

* This dose of atazanavir cannot be achieved with this formulation.

	sulfate)/Ritonavir 300 mg/100mg Tablets.	
ALPHA-1 ANDRENOCEPTOR ANTAGONISTS		
Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by atazanavir/ritonavir.	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and alfuzosin is **contraindicated** (see Contraindications)
ANTIARRHYTHMICS		
Amiodarone, Quinidine	Concentrations of amiodarone and quinidine may be increased when co-administered with atazanavir and ritonavir.	The concomitant use of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and amiodarone or quinidine is contraindicated (see Contraindications).
Systemic Lidocaine	Concentrations may be increased when co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.	Caution is warranted and clinical monitoring is recommended if intravenous lidocaine is administered for the treatment of acute ventricular arrhythmia.
Flecainide, Encainide, Propafenone	Ritonavir co-administration is likely to result in increased plasma concentrations of flecainide, encaininde and propafenone.	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and flecainide, encainide or propafenone is **contraindicated** (see Contraindications).
Digoxin (0.5 single IV dose/ ritonavir 300 mg BID (3 days)) (0.4 single oral dose / ritonavir 200 mg BID)	Digoxin AUC ↑ 86% Digoxin AUC ↑ 22%	Caution is warranted and clinical monitoring is recommended if Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and digoxin are co-administered. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops.
ANTI-ASTHMATICS		
Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected.	Concomitant use is not recommended.
Theophylline	An increased dose of theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.	Theophylline efficacy should be closely monitored if co-administrated with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
ANTINEOPLASTICS AND IMMUNOSUPPRESSANTS		
Antineoplastics		
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.

Vincristine, Vinblastine	Serum concentrations of vincristine or vinblastine may be increased when co-administered with ritonavir.	If Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is co-administered with vincristine or vinblastine, patients should be closely monitored for adverse events related to irinotecan.
Immunosuppressants		
Cyclosporine Tacrolimus Sirolimus Everolimus	Concentrations of these immunosuppressants may be increased when co-administered with atazanavir and ritonavir due to CYP3A4 inhibition.	More frequent therapeutic drug monitoring of these immunosuppressants is recommended until plasma levels have been stabilised.
ANTICOAGULANTS		
Warfarin	Co-administration with atazanavir and ritonavir has the potential to produce a decrease or, less often, an increase in INR (International Normalised Ratio).	It is recommended that the INR be monitored carefully during treatment with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, especially when commencing therapy.
CALCIUM CHANNEL BLOCKERS		
Bepridil	Serum concentrations of bepridil may be increased by atazanavir and ritonavir due to CYP3A4 inhibition.	As bepridil has a narrow therapeutic index, its co-administration with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is contraindicated (see Contraindications).
Verapamil	Serum concentrations of verapamil may be increased by atazanavir and ritonavir due to CYP3A4 inhibition.	Caution should be exercised if verapamil must be co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets due to the increased risk of AV-block. ECG monitoring should be considered.
Amlodipine, Nifedipine	An increase in the plasma concentrations of calcium channel antagonists are expected due to CYP3A4 inhibition.	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Diltiazem 180 mg QD / Atazanavir 400 mg QD	Diltiazem AUC ↑ 125%, C_{max} ↑ 198% Desacetyl-Diltiazem AUC ↑ 165%, C_{max} ↑ 121% No significant effect on atazanavir concentrations was observed. There was an increase	If diltiazem must be co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, an initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring, due to the increased risk of AV-block.

	in the maximum PR interval compared to atazanavir alone. Co-administration of diltiazem with atazanavir and ritonavir has not been studied.	
HMG-CoA REDUCTASE INHIBITORS		
Simvastatin Lovastatin	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with atazanavir and ritonavir may result in increased concentrations.	Co-administration of simvastatin or lovastatin with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is contraindicated, as this is likely to lead to a greater risk of rhabdomyolysis (see Contraindications). The use of another HMG-CoA reductase inhibitor which does not undergo metabolism by CYP3A such as pravastatin or fluvastatin is recommended.
Atorvastatin	Atorvastatin is metabolized by CYP3A4 and co-administration with atazanavir and ritonavir may result in increased concentrations.	The risk of myopathy including rhabdomyolysis may be increased with atorvastatin. If co-administered, the lowest possible initial dose of atorvastatin should be used, and the patient should be closely monitored for efficacy and safety (see Special warnings and precautions for use).
Fluvastatin, Pravastatin	The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with atazanavir and ritonavir.	If co-treatment with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Rosuvastatin	While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition.	When co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, the lowest possible doses of rosuvastatin should be administered.
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol 25 µg + norgestimate / Atazanavir 300 mg QD with ritonavir 100 mg QD)	Ethinyloestradiol AUC ↓ 19% Norgestimate AUC ↑85% The net effect of atazanavir with ritonavir is a decrease in ethinyloestradiol levels because	The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidaemia, acne and spotting), possibly affecting compliance. If an oral contraceptive is administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg

	of the inducing effect of ritonavir.	Tablets, it is recommended that the oral contraceptive contains at least 30 µg of ethinyloestradiol and that the patient is reminded of strict compliance with this contraceptive dosing regimen. Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternative reliable method of contraception is recommended.
OPIOIDS		
Fentanyl	Interaction with atazanavir and ritonavir not studied. Both inhibit CYP3A4 and as a result are expected to increase the plasma concentrations of fentanyl.	The combination of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with fentanyl should be avoided due to the potential for life-threatening adverse events, such as respiratory depression.
Methadone, stable maintenance dose / Atazanavir 400 mg QD	No significant effect on methadone concentrations was observed. Ritonavir (100 mg) has also been shown to have no significant effect on methadone concentrations.	No dosage adjustment is necessary.
Buprenorphine, QD, stable maintenance dose / Atazanavir 300 mg QD with ritonavir 100 mg QD	Buprenorphine AUC ↑ 67%, C_{min} ↑ 69% Norbuprenorphine AUC ↑ 105%, C_{min} ↑ 101%	Co-administration with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Pethidine, propoxyphene	Not studied.	Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine and propoxyphene. Co-administration of these drugs with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is therefore **contraindicated** (see Contraindications).
Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir.	Morphine doses should be titrated to adequate effect.
SEDATIVES		
Benzodiazepines		
Midazolam	Midazolam is extensively metabolized by CYP3A4, therefore co-administration may	Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets should not be co-administered with orally

	cause a large increase in the concentration of this benzodiazepine. 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.	administered midazolam (see Contraindications), whereas caution should be used with co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and parenteral midazolam. If Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting with 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.
Clorazepate, Diazepam, Estazolam, Flurazepam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam.	Co-administration of these drugs and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is **contraindicated** (see Contraindications).
Triazolam (0.125 mg single dose / ritonavir 200 mg, 4 doses)	Triazolam AUC ↑ > 2000%,	Co-administration of triazolam and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is **contraindicated** (see Contraindications).
Alprazolam (1 mg single dose / ritonavir 200 BID, 2 days)	Alprazolam AUC ↑ 150%. This interaction may be attenuated after a longer time on ritonavir, due to enzyme induction.	Caution is warranted especially during the first several days when alprazolam is co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Other		
Buspirone	An increase in the plasma concentration of buspirone is expected due to CYP3A4 inhibition by ritonavir.	Careful monitoring of therapeutic and adverse effects is recommended when buspirone is concomitantly administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
ANTIDEPRESSANTS		
Trazodone 50 mg single dose / ritonavir 200 mg BID	Trazodone AUC ↑ 140%, C_{max} ↑ 34%	If trazodone is co-administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.
ANTIPSYCHOTICS / NEUROLEPTICS		

Pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of pimozide.	Co-administration of pimozide and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is **contraindicated** (see Contraindications).
ANTICONVULSANTS		
Phenytoin	Phenytoin is an inducer of CYP3A.	Co-administration of phenytoin and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended, as exposure to atazanavir may decrease.
Carbamazepine	Carbamazepine is an inducer and a substrate of CYP3A.	Co-administration of carbamazepine and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended as exposure to atazanavir may decrease and exposure to carbamazepine may increase.
Phenobarbital	Phenobarbital is an inducer of CYP3A.	Co-administration of phenobarbital and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is not recommended, as exposure to atazanavir may decrease.
Valproic acid	Co-treatment with ritonavir may decrease valproic acid exposure due to enzyme induction of CYP2C9.	If Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and valproic acid are co-administrered, valproic acid effect and, if possible, plasma concentration should be monitored.
Lamotrigine (100 mg single dose / (atazanavir 300 mg QD with ritonavir 100 mg QD)	Lamotrigine AUC ↓ 32% C_{max} ↓ 6%	Lamotrigine and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets should be co-administered with caution. Monitor for lamotrigine efficacy.

CORTICOSTEROIDS		
Fluticasone propionate intranasal 50 µg 4 times daily for 7 days / ritonavir 100 mg capsules BID	Fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86%; greater effects may occur with inhalation. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; this could also occur with other corticosteroids metabolized via the CYP3A pathway, e.g. budesonide.	Concomitant administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with fluticasone or other inhaled corticosteroids (e.g. budesonide, mometasone) that are substrates of CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see Special warnings and precautions for use). The use of a corticosteroid which is not a substrate of CYP3A (e.g. beclomethasone) is recommended.
Dexamethasone	An increase in the plasma concentrations of dexamethasone can be expected due to CYP3A inhibition by ritonavir.	Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Prednisolone 20 mg / ritonavir 200 mg BID	Prednisolone (AUC) ↑ 28%	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
ANTIHISTAMINES		
Astemizole, Terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine.	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and either of these drugs is **contraindicated** (see Contraindications).
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.	No dosage adjustment is necessary.
Loratadine	An increase in the plasma concentrations of loratadine can be expected due to CYP3A inhibition by ritonavir.	Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		

Sildenafil Tadalafil Vardenafil	Sildenafil, tadalafil and vardenafil are metabolised by CYP3A4. Co-administration with atazanavir and ritonavir may result in increased concentrations of either of these agents and an increase in adverse events, including hypotension, visual changes, and priapism. Available data indicate that these effects are likely greater for vardenafil.	Dosage adjustment of sildenafil or tadalafil is necessary for co-administration of the PDE5 inhibitors with protease inhibitors. Dosing instructions for the respective medicinal products should be consulted. Patients should be warned about the possible side effects. Co-administration of vardenafil and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets is contraindicated.
PULMONARY ARTERIAL HYPERTENSION		
Sildenafil	Sildenafil is metabolized by CYP3A. Co-administration with atazanavir and ritonavir may result in increased concentrations of sildenafil and an increase in adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir/ritonavir.	A safe and effective dose in combination with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets has not been established for sildenafil when used to treat pulmonary arterial hypertension. Therefore, co-administration with sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated (see Contraindications).
Bosentan	Bosentan is a substrate of the Organic Anion Transport Protein (OATP) metabolized by CYP3A. Co-administration with atazanavir and ritonavir may result in increased concentrations of bosentan due to inhibition of OATP and CYP3A. Also, bosentan is an inducer of CYP3A which may decrease exposure of atazanavir.	Co-administration is not recommended. If co-administration is deemed necessary, when starting bosentan in patients already receivingAtazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets, use a bosentan dose of 62.5 mg once daily or every other day based on individual tolerability. When starting Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tabletsin patients already on bosentan, discontinue bosentan at least 36 h prior to starting Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and restart after at least 10 days at 62.5 mg once daily or every other day based on individual tolerability. The efficacy of HIV therapy should be appropriately monitored.
MISCELLANEOUS		
Ergot derivatives		

Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives.	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets and ergot derivatives is **contraindicated** (see Contraindications).
Sleeping agent		
Zolpidem (5 mg / ritonavir 200 mg 4 doses)	Zolpidem AUC ↑ 28% C_{max} ↑ 22%	Zolpidem and Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets may be co-administered with careful monitoring for excessive sedative effects.
Smoking cessation		
Bupropion (150 mg / ritonavir 100 mg BID)	Bupropion AUC ↓ 22% C_{max} ↓ 21% Bupropion is primarily metabolised by CYP2B6.	Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded if co administered with Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets.
Herbal Products		
St John's Wort	Concomitant use of St. John's wort with atazanavir (and ritonavir) may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to induction of CYP3A4.	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets with products containing St. John's wort is contraindicated (see Contraindications).

4.6 Pregnancy and lactation

Pregnancy

No increased risk of birth defects have been reported for atazanavir and ritonavir (www.apregistry.com). However, risks to the fetus cannot be ruled out.

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

Breastfeeding

It is not known whether atazanavir and ritonavir is excreted in human milk. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Atazanavir (as sulfate)/Ritonavir

300 mg/100mg Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions of moderate to severe intensity with possible or probable relationship to atazanavir and ritonavir have been reported. The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).

Cardiac disorders

Rare: Oedema, Palpitation
Unknown: QTc Prolongation, Torsade des pointes

Nervous system disorders

Common: Headache
Uncommon: Peripheral neuropathy, Syncope, Amnesia, Dizziness, Somnolence, Dysgeusia

Eye disorders

Common: Ocular icterus

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

Renal and urinary disorders

Uncommon: Nephrolithiasis (see Special warnings and precautions for use), Haematuria, Proteinuria, Pollakiuria
Rare: Kidney pain

Skin and subcutaneous tissue disorders

Common: Rash
Uncommon: Urticaria, Alopecia, Pruritus, Erythemia multiforme, Toxic skin eruptions, Drug rash with eosinophilia and Systemic symptoms (DRESS) syndrome
Rare: Stevens-Johnson syndrome , Eczema, Vasodilatation

Musculoskeletal and connective tissue disorders

Uncommon: Muscle atrophy, Arthralgia, Myalgia
Rare: Myopathy, Osteonecrosis (see Special warnings and precautions for use)

Metabolism and nutrition disorders

Uncommon: Weight decreased, Weight gain, Anorexia, Appetite increased
Unknown: Hyperglycaemia, Diabetes mellitus

Vascular disorders

Uncommon: Hypertension

General disorders and Administration site conditions

Common: Lipodystrophy syndrome (see Special warnings and precautions for use), Fatigue

Uncommon: Chest pain, Malaise, Pyrexia, Asthenia
Rare: Gait disturbance

Immune system disorders
Uncommon: Hypersensitivity
Unknown: Immune reconstitution syndrome (see Special warnings and precautions for use)

Hepatobiliary disorders
Common: Jaundice
Uncommon: Hepatitis
Rare: Hepatosplenomegaly
Unknown: Cholelithiasis, Cholecystitis, Cholestasis

Reproductive system and breast disorders
Uncommon: Gynaecomastia

Psychiatric disorders
Uncommon: Depression, Disorientation, Anxiety, Insomnia, Sleep disorder, Abnormal dream

Laboratory abnormalities
The most frequently reported laboratory abnormality in patients receiving regimens containing atazanavir+ritonavir and one or more NRTIs was elevated total bilirubin, predominantly elevated indirect (unconjugated) bilirubin. Among treatment-experienced patients treated with atazanavir 300 mg and ritonavir 100 mg once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among treatment-naive patients treated with atazanavir 300 mg and ritonavir 100 mg once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see Special warnings and precautions for use).

Other marked clinical laboratory abnormalities (Grade 3-4) reported in ≥ 2% of patients receiving regimens containing atazanavir and one or more NRTIs included: elevated creatine kinase (7%), elevated alanine aminotransferase (ALT) (5%), decreased neutrophils (5%), elevated aspartate aminotransferase (AST) (3%), and elevated lipase (3%).

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

4.9 Overdose
Human experience of acute overdose with atazanavir 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 Special warnings and precautions for use and Undesirable effects).

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paraesthesia, which resolved after the dose was decreased. A case of renal failure with eosinophilia has been reported.

There is no specific antidote for overdose with atazanavir and/or ritonavir. Treatment of overdose with atazanavir and/or ritonavir 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 and/or ritonavir could be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since

atazanavir and ritonavir are extensively metabolised by the liver and are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active susbstance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Protease Inhibitors
ATC codes: J05AE08 (Atazanavir), J05AE03 (Ritonavir)

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. Atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor.

Resistance

Antiretroviral treatment naive adult patients

In clinical trials of antiretroviral treatment naive 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 naive patients treated with ritonavir-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 2. *De novo* substitutions in treatment naive patients failing therapy with Atazanavir + Ritonavir (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 atazanavir/ritonavir and 7/26 lopinavir/ritonavir virologic failure patients, respectively.

Antiretroviral treatment experienced adult patients

In antiretroviral treatment experienced patients from studies, 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 3. *De novo* substitutions in treatment experienced patients failing therapy with Atazanavir + Ritonavir (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 PhenoSenseTM (Monogram Biosciences, South San Francisco, California, USA)

None of the de novo substitutions (see Table 3) are specific to atazanavir and may reflect re-emergence of archived resistance on atazanavir + ritonavir in the 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 naive adult patients

In a randomised, open-label, multicenter, prospective trial of treatment-naïve patients, atazanavir/ritonavir (300 mg/100 mg once daily) was compared to lopinavir/ritonavir (400 mg/100 mg twice daily), each in combination with fixed dose tenofovir/emtricitabine (300 mg/200 mg tablets once daily). In this study the atazanavir/ritonavir arm showed similar (non-inferior) antiviral efficacy compared to the lopinavir/ritonavir arm, with 78% of patients in the atazanavir/ritonavir arm achieving HIV RNA < 50 copies/ml at week 48, compared to 76% of patients in the lopinavir/ritonavir arm (ITT, Missing=failure). Results at 96 weeks of treatment demonstrated durability of antiviral activity.

In antiretroviral experienced adult patients

A randomised, multicenter trial compared atazanavir/ritonavir (300/100 mg once daily), atazanavir/saquinavir (400/1200 mg once daily), and lopinavir/ritonavir (400/100 mg fixed dose combination, twice daily), each in combination with tenofovir (see Interactions with other medicinal products and other forms of interaction and Undesirable effects) and one NRTI, in patients who had failed two or more prior regimens containing at least one PI, NRTI, and NNRTI. Overall, 13% patients in the atazanavir/ritonavir arm and 14% of 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 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. At 48 weeks the mean changes from baseline in HIV RNA levels for atazanavir/ritonavir and lopinavir/ritonavir were similar/ non-inferior (-1.93 $\log_{10}$ copies/ml for atazanavir/ritonavir and -1.87 $\log_{10}$ copies/ml for lopinavir/ritonavir), and the time-averaged difference was 0.13 $\log_{10}$ copies/ml (atazanavir/ritonavir -lopinavir/ritonavir). Treatment response was durable through 96 weeks. The combination of atazanavir and saquinavir was inferior to lopinavir and ritonavir.

5.2 Pharmacokinetic properties

Atazanavir

Absorption

The absolute bioavailability of atazanavir is unknown.

Following single dose administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets in healthy volunteers, the mean (±SD) atazanavir C_{max} value was 3683 (±928) ng/ml and the corresponding value for AUC was 33033 (±9141) ng.h/ml. The mean (±SD) atazanavir T_{max} value was 3.2 (±0.7) hours.

Effects of food on oral absorption: Co-administration of atazanavir and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of atazanavir 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. To enhance bioavailability and minimise variability, atazanavir 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

<u>*Impaired renal function*</u>: In healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for atazanavir with ritonavir in patients with renal insufficiency. atazanavir (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 Posology and method of administration and Special warnings and precautions for use.)

<u>*Impaired hepatic function*</u>: 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 Posology and method of administration, Contraindications and Special warnings and precautions for use).

Ritonavir

Absorption

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined.

Following single dose administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100mg Tablets in healthy volunteers, the mean (±SD) ritonavir C_{max} value was 1836 (±530) ng/ml and the corresponding value for AUC was 11479 (±3644) ng.h/ml. The mean (±SD) ritonavir T_{max} value was 4.3 (±0.4) hours.

Effects of food on oral absorption: Food slightly decreases the bioavailability of the ritonavir. Administration of a single 100 mg dose of ritonavir with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and C_{max}.

Distribution
The apparent volume of distribution (V_B/F) of ritonavir is approximately 20 - 40 L after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99% and is constant over the concentration range of 1.0 – 100 μg /ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.

Metabolism
Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Animal studies as well as *in vitro* experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent compound. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) (see Interactions with other medicinal products and other forms of interaction).

Elimination
Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

Special Populations
Patients with impaired liver function: After multiple dosing of ritonavir to healthy volunteers (500 mg twice daily) and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B, 400 mg twice daily) exposure to ritonavir after dose normalisation was not significantly different between the two groups.

Patients with impaired renal function: Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

5.3 Preclinical safety data
Atazanavir
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.

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 the 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 Special warnings and precautions for use and Undesirable effects). The potential for PR prolongation should be considered in cases of overdose (see Overdose).

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 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 long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only. This is considered 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.

Ritonavir
Ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Long term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Lactose monohydrate (166.80 mg of lactose per tablet), Crospovidone, Microcrystalline cellulose, Magnesium Stearate, Sodium Chloride, Sodium Stearyl Fumarate, Sorbitol, Maize Starch, Colloidal silicon dioxide, Copovidone, Sorbitan Monolaurate, film coat {Hypromellose, Polyethylene glycol 400, Polyethylene glycol 8000}

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container
HDPE bottle 30's.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

Reference list:

This text is based primarily on the European Summary of Product Characteristics (SmPC) for Reyataz (atazanavir sulfate), available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000494/WC500056380.pdf , as well as the the European SmPC for Norvir (ritonavir), which is available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000127/WC500028728.pdf

For further information, the following sources were also utilized:

Posology
Dosage in children
WHO: Antiretroviral therapy for HIV infection in infants and children: Towards universal access; Recommendations for a public health approach: 2010 revision:
http://www.who.int/hiv/pub/paediatric/infants2010/en/index.htm

Pregnancy and lactation
Breastfeeding
WHO: Guidelines on HIV and infant feeding 2010:
http://www.who.int/child_adolescent_health/documents/9789241599535/en/index.html

Drug interactions
Acosta et al. Antimicrob Agents Chemother 2007;51:3104-3110
Van Luin et al. AIDS 2010;24:1223-1226
The University of Liverpool HIV drug interactions database,
available at: http://www.hiv-druginteractions.org/
Tracleer, European SmPc, available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000401/human_med_001100.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124

Pharmacodynamic properties
Virology
Colonno et al. Antimicrob Agents Chemother 2003;47:1324-33
Winters et al. AIDS 2010;24:1593-1595
The Stanford HIV drug resistance database, available at: http://hivdb.stanford.edu/
Clinical
Molina et al. Lancet 2008;372:646-55
Molina et al. J Acquir Immune Defic Syndr 2010;323-332

Pharmacokinetic properties
von Hentiq et al. J Antimicrob Chemother 2008;62 :579-82
Anderson et al. J Antimicrob Chemother 2009;64:1071-79
Mirochnick et al. J Acquir Immune Defic Syndr 2011;56:412-419

Mfd. by:

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA.

Marketed by:
Matrix
(A division of Mylan Laboratories Limited)

August 2014