1. Product information

1.1. Summary of Product Characteristics

Summary of product characteristics is enclosed in the following pages.

1. Name of the medicinal product

Atazanavir and Ritonavir tablets 300 mg/100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atazanavir and Ritonavir tablets 300 mg/100 mg:

Each film coated tablet contains Atazanavir sulfate equivalent to Atazanavir 300 mg and Ritonavir USP 100 mg.

Formulation contains Lactose and Sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Atazanavir and Ritonavir tablets 300 mg/100 mg:

Yellow colored, oval shaped. film coated tablet debossed with 'L61' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indication

Atazanavir (as sulfate)/Ritonavir Tablets is indicated for the treatment of HIV-1 infected adults and children weighing at least 30 kg, in combination with other antiretroviral medicinal products.

The choice of fixed dose combination Atazanavir (as sulfate)/Ritonavir Tablets foruse in treatment-experienced patients should be based on treatment history of patients and, if available, also on individual viral resistance testing (see sections 4.4 and 5.1).

4.2. Posology and method of administration

Atazanavir (as sulfate)/Ritonavir Tablets should be prescribed by health care provider experienced in the treatment of HIV infection.

Adults: The recommended dose of Atazanavir (as sulfate)/Ritonavir Tablets is one tablet taken once daily with food. Atazanavir (as sulfate)/Ritonavir Tablets should beswallowed whole and not chewed, broken or crushed.

Patients weighing < 30 kg:
For these patients separate formulations containing lower amounts of atazanavir or

ritonavir areavailable.

Hepatic impairment: Atazanavir (as sulfate)/Ritonavir Tablets should be used withcaution in patients with mild hepatic impairment. Atazanavir (as sulfate)/Ritonavir Tablets is contraindicated in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

Renal impairment: No dosage adjustment is needed. Atazanavir (as sulfate)/Ritonavir Tablets is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients (see section 6.1). Atazanavir (as sulfate)/Ritonavir Tablets must not be administered to patients with decompensated liver disease (see sections 4.2 and 4.4).

Ritonavir is a potent inhibitor of CYP3A4- and CYP2D6- mediated drug metabolism. Furthermore, atazanavir and ritonavir are themselves substrates for CYP3A4 isoform of cytochrome P450. The following medicines are contraindicated when Atazanavir (as sulfate)/Ritonavir Tablets is used due to the risk of adverse effects or loss of efficacy due to drug-drug interactions (seealso sections 4.4. and 4.5.).

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 (see section 4.5).
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene, thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
Antiarrhythmics	Amiodarone, bepridil, encainide, flecanide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecanide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentration of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 4.5)
	Clozapine, pimozide	Increased plasma concentrations of clozapine and 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.
GI motility agent	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 sections 4.4 and 4.5).
PDE5 inhibitors	Avanafil	Increased plasma concentrations of avanafil (see section 4.4 and 4.5)
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include

		hypotension and syncope). See section 4.4 and section 4.5 for co-administration 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 section 4.5.)
Antimycobacterial	Rifampicin	Decreased plasma concentration and reduced clinical effect of atazanavir and ritonavir (see also section 4.5.)
Herbal Preparation	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 transmissionof HIV to others through sexual contact or contamination with blood. Patients should continue to takeappropriate precautions.

Opportunistic infections: Patients taking Atazanavir (as sulfate)/Ritonavir 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 sections 4.2 and 4.3). The safety and efficacy of Atazanavir (as sulfate)/Ritonavir 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 Tablets is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

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 section 4.8).

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 theabsence 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 beenestablished.

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 inhibitionof UDP-glucuronosyl transferase (UGT), have occurred in patients receiving atazanavir (see section 4.8). 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 Tablets should be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it mayresult 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 Atazanavir (as sulfate)/Ritonavir Tablets and indinavir have not been studied and co-administration of these medicinal products is not recommended (see section4.5).

Nephrolithiasis: Nephrolithiasis has been reported in patients receiving atazanavir (see section 4.8). Ifsigns or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment with Atazanavir (as sulfate)/Ritonavir Tablets may be considered.

Cholelithiasis: Cholelithiasis has been reported in patients receiving atazanavir (see section 4.8). Some patients required hospitalization for additional management and some had complications.

If signs or symptoms of cholelithiasis occur, temporary interruption or discontinuation of treatment maybe 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 Tablets should be used with caution and only if the benefits

exceed the risk (see section 5.1).

Particular caution should be used when prescribing Atazanavir (as sulfate)/Ritonavir 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 sections 4.8 and 5.3).

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 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 Tablets. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. Atazanavir (as sulfate)/Ritonavir Tablets should be discontinued if severe rash develops.

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

Interactions with other medicinal products

Atazanavir (as sulfate)/Ritonavir Tablets is a co-formulation of atazanavir and ritonavir. The latter is a very strong inhibitor of CYP3A4 and an inducer of hepatic drug metabolising enzymes. Atazanavir is metabolised principally by CYP3A4 and drug levels may be reduced when co-administering CYP3A4 inducers. For these reasons Atazanavir (as sulfate)/Ritonavir 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 section 4.3. Further combinations which should be avoided include, but are not limited to, NNRTIs, hormonal contraceptives, some HMG-CoA reductase inhibitors and some corticosteroids (see section 4.5.) 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 Tablets andproton pump inhibitors is not recommended (see section 4.5.)

Excipients
Atazanavir (as sulfate)/Ritonavir Tablets contains lactose. Patients with rare hereditary problems of galactose 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 primarilymetabolised by CYP3A4 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 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 particularly ergotamine and dihydroergotamine (see section 4.3).

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

NNRTIs: Co-administration of Atazanavir (as sulfate)/Ritonavir 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 Tablets.
Rifampicin: Co-administration of Atazanavir (as sulfate)/Ritonavir Tablets with rifampicin is contraindicated. Rifampicin in combination with atazanavir and ritonavir causes largedecreases 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 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 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 Tablets and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and table below).

Antifungals: Co-administration of voriconazole and Atazanavir (as sulfate)/Ritonavir 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 isincreased irrespective of cause.

Co-administration of Atazanavir (as sulfate)/Ritonavir Tablets with proton pump inhibitors is not recommended (see table below). If the combination of Atazanavir (as sulfate)/Ritonavir 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 Tablets in combination with tenofovir and an H2-receptor antagonist should be avoided (see table below).

Hormonal contraceptives: If an oral contraceptive is administered with Atazanavir (as sulfate)/Ritonavir 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 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 Tablets with fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as budesonide and triamcinolone, 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).

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

wereconducted 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.

Other interactions

Interactions between Atazanavir (as sulfate)/Ritonavir Tablets 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 1 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).

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

Medicinal products by therapeuticarea	**Interaction**	**Recommendations concerningco-administration**
ANTI-RETROVIRALS		
Protease inhibitors: The co-administration of Atazanavir (as sulfate)/Ritonavir Tablets and otherprotease 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 infectedpatients	Atazanavir AUC: ↑250% (↑144% ↑403%)* Atazanavir C_{max}: ↑120% (↑56% ↑211%)* Atazanavir C_{min}: ↑713% (↑359% ↑1339%)* * 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 usedas a booster of atazanavir pharmacokinetics.
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT	Co-administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets and Indinavir is not recommended (see section 4.4).
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine 150mg twice daily +zidovudine 300mg twice daily (azatanavir 400mg 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 NRTs, the co-administration of these medicinal products and Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets is not expected to significantly alter the exposure of the co-administered medicinalproducts.
Abacavir	The co-administration of abacavir and Atazanavir (as sulfate)/Ritonavir Tablets is not expected to significantly alter the exposure of abacavir	

Medicinal products by therapeuticarea	Interaction	Recommendations concerningco-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 Atazanavir (as sulfate)/Ritonavir Tablets taken with food. The co-administration of stavudine with Atazanavir (as sulfate)/Ritonavir Tablets is not expected to significantly alter the exposure of stavudine.
Didanosine (enteric coated capsules)400 mg single dose (atazanavir 300 mg once daily withritonavir 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.	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (atazanavir 400 mg once daily withritonavir 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 with Atazanavir (as sulfate)/Ritonavir Tablets is not recommended (see section 4.4).

Medicinal products by therapeuticarea	**Interaction**	**Recommendations concerningco-administration**
Nevirapine 200 mg twice daily (atazanavir 400 mg once daily withritonavir 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 Atazanavir (as sulfate)/Ritonavir Tablets 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 with Atazanavir (as sulfate)/Ritonavir Tablets 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 forraltegravir.

Medicinal products by therapeuticarea	Interaction	Recommendations concerningco-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 Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets, high doses of ketoconazole and itraconazole (>200 mg/day) are not recommended.
Itraconazole	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, REYATAZ/ritonavir is expected to increase ketoconazole or itraconazole concentrations.	

Medicinal products by therapeuticarea	**Interaction**	**Recommendations concerning co-administration**
Voriconazole 200 mg twice daily (atazanavir 300 mg/ritonavir 100 mgonce daily) Subjects with at least one functionalCYP2C19 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 Atazanavir (as sulfate)/Ritonavir Tablets 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 recomendations 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.

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-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.	
Fluconazole 200 mg once daily (atazanavir 300 mg and ritonavir 100 mg once daily)	Atazanavir and fluconazole concentrations were not significantly modified when Atazanavir (as sulfate)/Ritonavir Tablets was co- administered with fluconazole.	No dosage adjustments are neededfor fluconazole and Atazanavir (as sulfate)/Ritonavir Tablets.

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-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% ↑1361%) ** 25-O-desacetyl-rifabutin C_{max} ↑677% (↑513% ↑883%) ** 25-O-desacetyl-rifabutin C_{min} ↑1045% (↑715% ↑1510%) ** ** 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 Atazanavir (as sulfate)/Ritonavir Tablets, 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 toa risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for Atazanavir (as sulfate)/Ritonavir Tablets.

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-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 Atazanavir (as sulfate)/Ritonavir Tablets or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and Atazanavir (as sulfate)/Ritonavir Tablets is contraindicated (see section 4.3).
ANTIPSYCHOTICS		
Quetiapine	Due to CYP3A4 inhibition by Atazanavir (as sulfate)/Ritonavir Tablets, concentrations of quetiapine are expected to increase.	Co-administration of quetiapine with Atazanavir (as sulfate)/Ritonavir Tablets is contraindicated as Atazanavir (as sulfate)/Ritonavir Tablets may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see section 4.3).
ACID REDUCING AGENTS		
H2-Receptor antagonists		
Without Tenofovir disoproxil fumarate		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily		For patients not taking tenofovir disoproxil fumarate, if Atazanavir (as sulfate)/Ritonavir Tablets and H2-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg twice daily should not be exceeded. If a higher dose of an H2- receptor antagonist is required (e.g., famotidine 40 mg twice daily or equivalent) an increase of the Atazanavir (as sulfate)/Ritonavir Tablets dose 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%)	

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
With Tenofovir disoproxil fumarate 300 mg once daily		
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 Atazanavir (as sulfate)/Ritonavir Tablets with both tenofovir disoproxil fumarate and an H_2-receptor antagonist are co- administered, a dose increase of Atazanavir (as sulfate)/Ritonavir Tablets to 400 mg/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%) *	
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 Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets to 400 mg / 100 mg; doses of proton pump inhibitors comparable to

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
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 Atazanavir (as sulfate)/Ritonavir Tablets to (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.	omeprazole 20 mg should not beexceeded (see section 4.4).
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 Atazanavir (as sulfate)/Ritonavir Tablets.	Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets.	Co-administration of alfuzosin with Atazanavir (as sulfate)/Ritonavir Tablets is contraindicated (see section 4.3)

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
ANTICOAGULANTS		
Warfarin	Co-administration with Atazanavir (as sulfate)/Ritonavir Tablets has the potential to increase or decrease warfarin concentrations.	It is recommended that the International Normalised Ratio (INR) be monitored carefully during treatment with Atazanavir (as sulfate)/Ritonavir Tablets especially when commencing therapy.
ANTIEPILEPTICS		
Carbamazepine	Atazanavir (as sulfate)/Ritonavir Tablets may increase plasma levels of carbamazepine due to CYP3A4 inhibition. Due to carbamazepine inducing effect, a reduction in Atazanavir (as sulfate)/Ritonavir Tablets exposure cannot be ruled out.	Carbamazepine should be used with caution in combination with Atazanavir (as sulfate)/Ritonavir Tablets If necessary, monitor carbamazepine serum concentrations and adjust the dose accordingly. 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 Atazanavir (as sulfate)/Ritonavir Tablets exposure cannot be ruled out.	Phenobarbital and phenytoin should be used with caution in combination with Atazanavir (as sulfate)/Ritonavir Tablets. When Atazanavir (as sulfate)/Ritonavir Tablets is co-administered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required. Close monitoring of patient'svirologic response should be exercised.
Lamotrigine	Co-administration of lamotrigine and Atazanavir (as sulfate)/Ritonavir Tablets may decrease lamotrigine plasma concentrations due to UGT1A4 induction.	Lamotrigine should be used with caution in combination with Atazanavir (as sulfate)/Ritonavir Tablets. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly.
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If Atazanavir (as sulfate)/Ritonavir Tablets is co- administered with irinotecan, patients should be closely monitored for adverse events relatedto irinotecan.
Immunosuppressants		
Cyclosporin **Tacrolimus** **Sirolimus**	Concentrations of these immunosuppressants may be increased when co-administered with Atazanavir (as sulfate)/Ritonavir Tablets due toCYP3A4 inhibition.	More frequent therapeutic concentration monitoring of these medicinal products is recommendeduntil plasma levels have been stabilised.
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Amiodarone, **Systemic lidocaine,** **Quinidine**	Concentrations of these antiarrhythmics may be increased when co-administered with Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets	Caution is warranted and therapeutic concentration monitoring is recommended whenavailable. The concomitant use ofquinidine is contraindicated (see section 4.3).
Calcium channel blockers		
Bepridil	Atazanavir (as sulfate)/Ritonavir Tablets should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil iscontraindicated (see section 4.3)

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
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 Atazanavir (as sulfate)/Ritonavir Tablets 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 neededand ECG monitoring.
Verapamil	Serum concentrations of verapamil may be increased by Atazanavir (as sulfate)/Ritonavir Tablets due to CYP3A4 inhibition.	Caution should be exercised whenverapamil is co-administered with Atazanavir (as sulfate)/Ritonavir Tablets
CORTICOSTEROIDS		

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
Fluticasone propionate intranasal 50 µg 4 times daily for 7 days (ritonavir 100 mg capsules twice daily)	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.	Co-administration of Atazanavir (as sulfate)/Ritonavir Tablets and these glucocorticoids 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.
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		
Sildenafil, tadalafil, vardenafil	Sildenafil, tadalafil and vardenafil are metabolised by CYP3A4. Co-administration with Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets (see section 4.4). Also see PULMONARY ARTERIAL HYPERTENSION in this table for further information regarding co-administration of Atazanavir (as sulfate)/Ritonavir Tablets with sildenafil.
HERBAL PRODUCTS		

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-administration
St. John's wort (Hypericum perforatum)	Concomitant use of St. John's wort with Atazanavir (as sulfate)/Ritonavir Tablets with sildenafil 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 Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. Analternate reliable method of contraception is recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerningco-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 LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Simvastatin **Lovastatin**	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with Atazanavir (as sulfate)/Ritonavir Tablets may result in increased concentrations.	Co-administration of simvastatin or lovastatin with Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets 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.
INHALED BETA AGONISTS		
Salmeterol	Co-administration with Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets 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 Atazanavir (as sulfate)/Ritonavir Tablets warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		

Sildenafil	Co-administration with Atazanavir (as sulfate)/Ritonavir Tablets 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 /ritonavir.	A safe and effective dose in combination with Atazanavir (as sulfate)/Ritonavir Tablets 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).

4.6 Fertility, pregnancy and lactation

Fertility

No human data on the effect of atazanavir and ritonavir on fertility are available. Animal studies donot indicate harmful effects of atazanavir and ritonavir on fertility (see section 5.3).

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 prepartumperiod, additional monitoring and alternative therapy to atazanavir should be considered.

Breastfeeding

Atazanavir and ritonavir have been detected 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

Patients should be informed that dizziness has been reported during treatment with Atazanavir (assulfate)/Ritonavir Tablets (see section 4.8).

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: uncommon: torsade des pointes
rare: QTc prolongation, oedema, palpitation

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 section 4.4), cholelithiasis, cholestasis, haematuria, proteinuria,pollakiuria, interstitial nephritis, chronic kidney disease rare: kidney pain
Skin and subcutaneous tissue disorders:	common: rash uncommon: urticaria, alopecia, pruritus, erythema 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
Metabolism and nutrition disorders	uncommon: weight decreased, weight gain, anorexia,appetite increased unknown: hyperglycaemia, diabetes mellitus
Vascular disorders:	uncommon: hypertension
General disorders andadministration site conditions:	common: lipodystrophy syndrome (see section 4.4), fatigue uncommon: chest pain,malaise, pyrexia, asthenia rare: gait disturbance
Immune system disorders:	uncommon: hypersensitivity unknown: Immune reconstitution syndrome (see section 4.4)
Hepatobiliary disorders:	common: jaundice uncommon: hepatitis, cholelithiasis, cholestasis rare: hepatosplenomegaly, cholecystitis
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, reported predominantly aselevated 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 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 section 4.4).

Other marked clinical laboratory abnormalities (Grade 3-4) reported in ≥ 2% of patients receivingregimens containing atazanavir 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 atazanavir experienced concurrent Grade 3-4 ALT/AST andGrade 3-4 total bilirubin elevations.

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 chronicviral 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 atazanavir 300 mg and ritonavir 100 mg 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 to the marketing authorisation holder, or, if available, via the national reporting system.

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 sections 4.4 and 4.8).

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 wasdecreased. 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 substance.

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 formationof mature virions and infection of other cells. Atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to the production of HIV particles with immature morphology that are unable toinitiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.
Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a studywith clinical endpoints. However, due to ritonavir's metabolic inhibitory properties its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice (see section 4.2).

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 naive 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. In clinical trials, the efficacy of atazanavir with ritonavir was reduced in patients with viral strains harbouring ≥4 protease inhibitor resistance mutations.

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 disoproxil fumarate (see sections 4.5 and 4.8) 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/100 mg Tablets in healthy volunteers, the mean (±SD) atazanavir C_{max} value was 4213 (±1174) ng/ml and the corresponding value for AUC was 45049 (±13108) ng.h/ml. The mean (±SD) atazanavir Tmax valuewas 4.63 (±1.43) 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. 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 atazanavir 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, 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 14C-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 alight 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 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 sections 4.2 and 4.4.)

Hepatic impairment: Atazanavir is metabolised and eliminated primarily by the liver. Atazanavir (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.

Ethnicity: A population pharmacokinetic analysis of samples from Phase II clinical trials indicated noeffect of ethnicity on the pharmacokinetics of atazanavir (as sulfate).

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.

Ritonavir

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

Following single dose administration of Atazanavir (as sulfate)/Ritonavir 300 mg/100 mg Tablets in healthy volunteers, the mean (±SD) ritonavir C_{max} value was 2020 (±537) ng/ml and the corresponding value for AUC was 14194 (±4849) ng.h/ml. The mean (±SD) ritonavir T_{max} value was4.17 (±0.80) 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 of20-23% 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 isconstant over the concentration range of 1.0 – 100 □g /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 wellas *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 proteaseinhibitors (and other products metabolised by CYP3A4) (see section 4.5).

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 foundto 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 differentbetween the two groups.

Patients with impaired renal function: Ritonavir pharmacokinetic parameters have not been studied inpatients 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 (APD90) 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 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 noeffects 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

Dicalcium phosphate anhydrous /Calcium hydrogen phosphate, colloidal silicon dioxide, copovidone, crospovidone, lactose monohydrate, magnesium stearate, sodium stearyl fumarate, sorbitan monolaurate, and Ferric oxide.

Film-coating:

Iron oxide yellow, Macrogol /PEG, Hypromellose and Titanium dioxide.

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 package. Keep the bottle tightly closed.

6.5 Nature and contents of container

300 mg/100 mg

30's Count: 85CC HDPE Bottle, 33 mm - 400 ARGUS CR Closure with TEKNIPLEX HS 123 induction sealing wad with silica gel canister 1g.

90's Count: 200CC HDPE Bottle, CAP 38 mm-400 ARGUS CR Closure with TEKNIPLEX HS 123 induction sealing wad with silica gel canister 2g.

6.6 Special precautions for disposal

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

7 Supplier

Laurus Labs Limited
2nd Floor, Serene Chambers, Road No.-7
Banjara Hills, Hyderabad – 500034.

Manufacturer:
Laurus Labs Limited, (Unit-2),
Plot No:19, 20 & 21,Western Sector, APSEZ,
Gurajapalem Village, Rambilli Mandal,
Anakapalli-District-531011,
Andhra Pradesh, India.

8 WHO PREQUALIFICATION REFERENCE NUMBER

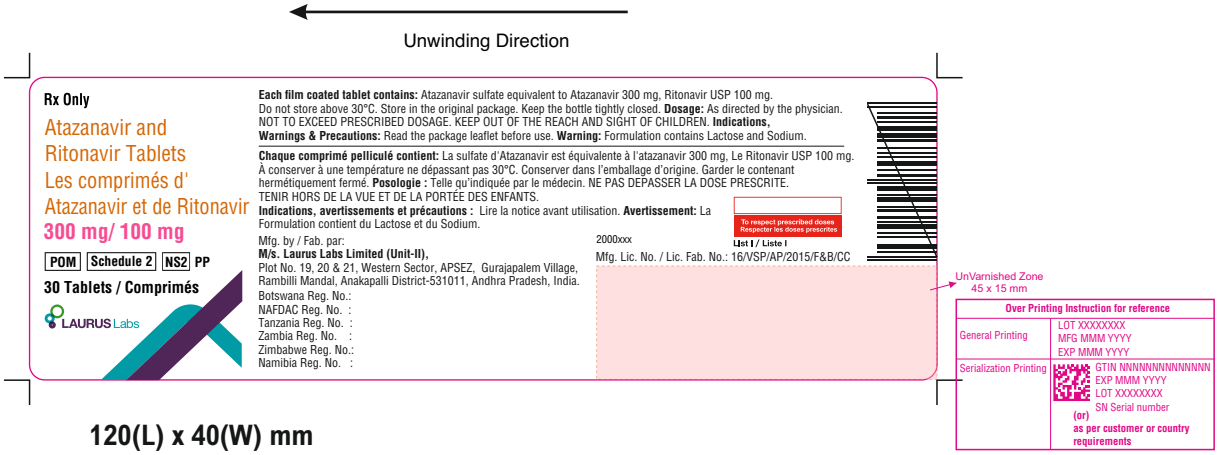
9 DATE OF PREQUALIFICATION

10 DATE OF REVISION OF THE TEXT

November 2023

1.2. Labeling (immediate and outer label)

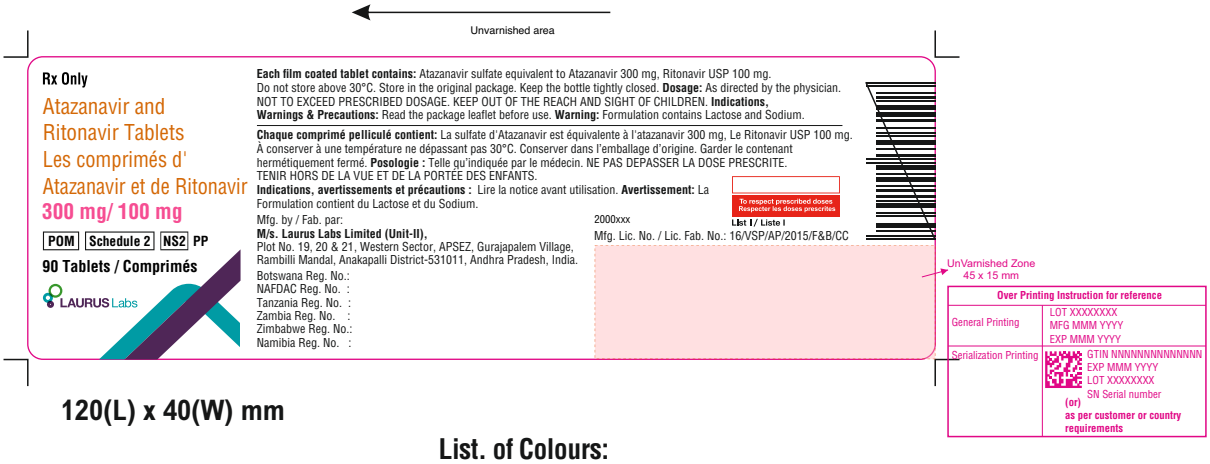
A mock up Label is enclosed overleaf.



120(L) x 40(W) mm

List. of Colours:

- Pantone 320 C
- Pantone 525 C
- Pantone 362 C
- Pantone 485 C
- Pantone 717 C
- Pantone 212 C
- Black



120(L) x 40(W) mm

List. of Colours:

- Pantone 320 C
- Pantone 525 C
- Pantone 362 C
- Pantone 485 C
- Pantone 717 C
- Pantone 212 C
- Black

1.3. Patient Information Leaflet (PIL) or Package Insert

Package leaflet is enclosed overleaf.

Package leaflet: Information for the user

Atazanavir (as sulfate) and Ritonavir tablets 150 mg/50 mg 300 mg/100 mg and

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, please ask your health care provider.
- 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 health care provider. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What atazanavir (as sulfate) and ritonavir tablets is and what it is used for

The main active ingredient of Atazanavir (as sulfate) and Ritonavir tablets is atazanavir, which belongs to a class of antiviral medicines called protease inhibitors. Atazanavir (as sulfate) and Ritonavir tablets also contains ritonavir, which is also a protease inhibitor, and which is used together with atazanavir to increase its effectiveness. Atazanavir (as sulfate) and Ritonavir tablets is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children weighing 30 kg or more, in combination with other antiretroviral medicinal products.

Atazanavir (as sulfate) and Ritonavir tablets works by reducing the amount of HIV in your body and this in turn, strengthens your immune system. In this way Atazanavir (as sulfate) and Ritonavir tablets reduces the risk of developing illnesses linked to HIV infection and raises the CD4 (T) cell count. CD4 cells are a type of white blood cells that play an important role in maintaining a healthy immune system to help fight infection.

This medicine is not a cure for HIV infection. While taking Atazanavir (as sulfate) and Ritonavir tablets you may still develop infections or other illnesses associated with HIV infection.

2. What you need to know before you take atazanavir (as sulfate) and ritonavir tablets

Do not take Atazanavir (as sulfate) and Ritonavir tablets if you

- are allergic (hypersensitive) to atazanavir, ritonavir or any of the other ingredients of

Atazanavir (as sulfate) and Ritonavir tablets (see section 6, What Atazanavir (as sulfate) and Ritonavir tablets contains);

- have severe liver disease.
- are currently taking any of the following medicines:
    - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
    - amiodarone, bepridil, encainide, flecainide, propafenone, quinidine (used to correct irregular heartbeats);
    - dihydroergotamine, ergotamine (used to treat migraine headache);
    - ergonovine, methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion);
    - clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety);
    - clozapine, pimozide, (used to treat abnormal thoughts or feelings);
    - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
    - lurasidone (used to treat depression);
    - ranolazine (used to treat chronic chest paint [angina]);
    - pethidine, propoxyphene (used to relieve pain);
    - cisapride (used to treat gastric reflux, sometimes called heartburn);
    - pimozide (used to treat schizophrenia);
    - quinidine or bepridil (used to correct heart rhythm);
    - rifampicin (used to treat tuberculosis);
    - simvastatin, lovastatin (used to lower blood cholesterol);
    - alfuzosin (used to treat enlarged prostate gland);
    - fusidic acid (used to treat bacterial infections);
    - sildenafil if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without this disease may use sildenafil for impotence (erectile dysfunction) under their health care provider's supervision (see the section on "Other medicines and Atazanavir (as sulfate)/Ritonavir tablets");
    - avanafil or vardenafil (used to treat erectile dysfunction);
    - products containing St John's wort (*Hypericum perforatum*) as this may stop Atazanavir (as sulfate) and Ritonavir tablets from working properly. St John's wort is often used in herbal medicines that you can buy without a prescription.

If you are currently taking any of the above medicines, ask your health care provider about switching to a different medicine while you are taking Atazanavir (as sulfate) and Ritonavir tablets. Often, there are other medicines you can take instead.

Also read the list of medicines under 'Other medicines and Atazanavir (as sulfate) and Ritonavir tablets' for use with certain other medicines which require special care.

Warnings and precautions

General:

You will need to take Atazanavir (as sulfate) and Ritonavir tablets every day. This

medicine helps to control your condition, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease (e.g. opportunistic infections). These may require specific and sometimes preventive treatment. You should keep in regular contact with your health care provider. Do not stop taking your medicine without first talking to your health care provider.

Treatment with Atazanavir (as sulfate) and Ritonavir tablets has not been shown to eliminate the risk of passing HIV infection on to others by sexual contact or by blood transfer. Appropriate precautions (e.g. use of condom) should be taken to prevent passing on the disease to others.

Tell your health care provider:
- about any past or present medical problems, including liver disease due to cirrhosis
- if you have kidney problems (including back pain with or without blood in your urine)
- if you have allergies
- if you have diabetes
- if you have haemophilia.
- if you are taking oral contraceptives ("the Pill") to prevent pregnancy
- if you are taking omeprazole or other proton pump inhibitors; or famotidine or other H_2- receptor antagonists (used to treat diseases related to the acid in the stomach)

It is important that your health care provider knows about all your symptoms even when you think they are not related to HIV infection.

Liver disease/hepatitis: Please tell your health care provider if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk of severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function. If you have liver disease, your health care provider will decide whether you may be treated with Atazanavir (as sulfate) and Ritonavir tablets.
Patients with liver disease being treated with Atazanavir (as sulfate) and Ritonavir tablets will be monitored closely for side effects. Talk to your health care provider if you are not sure.

Fat distribution: Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your health care provider if you notice changes in your body shape.

Bone problems: Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue).

Your risk of developing this disease may be higher:
- if your immune system is severely compromised,
- if you have been taking combination antiretroviral therapy for a long time,
- if you drink alcohol regularly,
- if you use corticosteroids (certain medicines suppressing your immune system),
- if you are overweight.

If you notice joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement, inform your health care provider.

Immune Reactivation Syndrome: 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 health care provider immediately.

Hyperbilirubinaemia and jaundice: An increase in the level of bilirubin in the blood may occur in patients receiving Atazanavir (as sulfate) and Ritonavir tablets. The signs may be a mild yellowing of the skin or eyes (jaundice). If you notice any of these symptoms please inform your health care provider.

Skin rash: Serious skin rash has been reported in patients taking Atazanavir (as sulfate) and Ritonavir tablets. If you develop a rash inform your health care provider immediately.

Heart rhythm changes: If you notice a change in the way your heart beats, please inform your health care provider.

Other medicines and Atazanavir (as sulfate) and Ritonavir tablets

It is important that you tell your health care provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of Atazanavir (as sulfate) and Ritonavir tablets , or Atazanavir (as sulfate) and Ritonavir may affect their action (see also above, section 'Do not take Atazanavir (as sulfate) and Ritonavir tablets, if you'). Side effects of either medicine may become worse and/or the medicines may become less effective.

Sometimes your health care provider may decide to adjust the dose of Atazanavir (as sulfate) and Ritonavir tablets or of the other drug. Examples of drugs that are or may be unsuitable to take together with Atazanavir (as sulfate) and Ritonavir tablets, or where dose adjustments may be necessary, include:

- medicines commonly used to treat allergy symptoms (e.g. astemizole, terfenadine),
- pimozide, a medicine used to treat abnormal thoughts or feelings,
- medicines used to correct irregular heartbeats (e.g. amiodarone, bepridil, encainide, flecainide, propafenone, quinidine),
- medicines used to treat migraine headache (e.g. dihydroergotamine, ergotamine),
- medicines used to stop excessive bleeding that may occur following childbirth or an abortion (e.g. ergonovine, methylergonovine),
- medicines to treat excess stomach acid, reflux esophagitis (heartburn) or ulcers (e.g. omeprazole, famotidine, antacids),
- cisapride, a medicine used to relieve certain stomach problems,
- medicines to treat malaria (e.g. lumefantrine, quinine),

- medicines to treat tuberculosis (TB; e.g. bedaquiline, delamind, rifampicin, rifabutin),
- medicines to treat fungal infections (e.g. itraconazole, fluconazole, voriconazole),
- medicines to supress the body's immune response (e.g. after organ transplantation, such as cyclosporine),
- other medicines against HIV (e.g. didanosine, tenofovir disoproxil fumarate, nevirapine, efavirenz),
- medicines to lower cholesterol (e.g. atorvastatin),
- corticosteroids (e.g. fluticasone, triamcinolone; for the treatment of inflammation and other diseases, such as asthma or rheumathoid arthritis),
- medicines to treat erectile dysfunction ("impotence"; e.g. sildenafil, tadalafil),
- medicines used to treat pulmonary arterial hypertension (e.g. riociguat, sildenafil, bosentan)
- medicines to prevent blood clots (e.g. vorapaxar, warfarin),
- calcium channel blockers (medicines to treat high blood pressure, e.g. diltiazem, verapamil),
- sedative agents (medicines used to treat anxiety and to help you sleep, e.g. triazolam, midazolam [given by injection]),
- hormonal contraceptives (e.g. "the Pill")
- medicines to treat bacterial infections (e.g. clarithromycin, erythromycin, sulphamethoxazole/trimethoprim, fusidic acid)
- alfuzosin, a medicine used to treat enlarged prostate gland
- products containing St John's wort (*Hypericum perforatum*)
- medicines used to relieve pain (e.g. pethidine, propoxyphene)
- medicines used to treat asthma (e.g. salmeterol, theophylline).
- afatinib, ceritinib, dasatinib, irinotecan, nilotinib, vincristine and vinblastine, medicines used to treat cancer
- trazodone, a medicine used to treat depression,
- medicines used to treat seizures (e.g. phenytoin, carbamazepine, phenobarbital, valproic acid, lamotrigine),
- bupropion, a medicine used for smoking cessation.

Atazanavir (as sulfate) and Ritonavir tablets with food and drink

Atazanavir (as sulfate) and Ritonavir tablets must be taken with food.

Pregnancy

If you become pregnant, or are planning to become pregnant, you must contact your health care provider to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

Be sure to tell your health care provider immediately if you are or may be pregnant.

Breastfeeding

If you are interested in breastfeeding your baby, you should discuss the risks and benefits with your healthcare provider.

Driving and using machines

No studies on the effects of Atazanavir (as sulfate) and Ritonavir tablets on the ability to drive and use machines have been performed. However, you should take into account the state of your health and the possible side effects of Atazanavir (as sulfate) and Ritonavir tablets before considering driving or using machines.

Atazanavir (as sulfate) and Ritonavir tablets contains lactose
If you have been told by your health care provider that you have an intolerance to some sugars, contact your health care provider before taking this medicinal product.

3. How to take atazanavir (as sulfate) and ritonavir tablets

Always take Atazanavir (as sulfate) and Ritonavir tablets exactly as your health care provider has told you.
In adults and children weighing 30 kg or more, the recommended dose is one tablet of Atazanavir (as sulfate) and Ritonavir tablets once daily. Atazanavir (as sulfate) and Ritonavir tablets must be taken with food.
Atazanavir (as sulfate) and Ritonavir tablets should be swallowed whole and not chewed, broken or crushed.
Other formulations containing less atazanavir and ritonavir are available for dosing in patients weighing less than 30 kg.
Atazanavir (as sulfate) and Ritonavir tablets should always be taken in combination with other antiretroviral medication; please make sure to follow the instructions within the supplied patient information leaflets.
Do not stop taking Atazanavir (as sulfate) and Ritonavir tablets, because reducing or missing doses will increase the risk of the HIV becoming resistant to atazanavir, in which case treatment with this medicine and possibly others will become ineffective. You should check with your health care provider if you are not sure.

If you take more Atazanavir (as sulfate) and Ritonavir tablets than you should

If you have taken too many tablets or if someone accidentally swallows some, you should contact your health care provider, or the nearest hospital emergency department for further advice.

If you forget to take Atazanavir (as sulfate) and Ritonavir tablets

If you forget to take a dose of your medicine, take it as soon as you remember, and then continue as before. If your next dose is due in less than 6 hours, do not take the forgotten dose, but take the next regular dose when it is due. Do not take a double dose to make up for forgotten individual doses.

If you have any further questions on the use of this product, ask your health care provider.

4. Possible side effects

Like all medicines, Atazanavir (as sulfate) and Ritonavir tablets can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Atazanavir (as sulfate) and Ritonavir tablets, or those caused by any other medicines you may be taking at the same time, or by the HIV disease. For this reason, it is important that you inform your health care provider of any change in your health.

Common side effects (may affect up to 1 in 10 people)

- fat redistribution with increased fat in the abdomen (belly) and internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump').
- headache
- yellow whites of eyes (ocular icterus)
- jaundice (yellow skin)
- nausea
- vomiting
- diarrhoea
- an uncomfortable feeling in the stomach or belching after eating
- abdominal pain
- elevated bilirubin levels in the blood
- rash
- weakness/fatigue

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

- peripheral neuropathy (numbness, weakness, tingling or pain in the arms and legs)
- asthenia (unusual tiredness or weakness)
- decreased or abnormal skin sensation
- fainting
- loss of memory
- dizziness
- sleepiness
- altered sense of taste
- shortness of breath
- inflammation of the stomach (gastritis), liver (hepatitis), or pancreas (pancreatitis)
- swollen abdomen
- mouth ulcers and cold sores
- wind (flatulence)
- dry mouth
- increased frequency of urination
- kidney stones
- blood and/or excess protein in the urine
- itching of the skin (pruritus)
- hives
- hair loss
- serious skin rashes (allergic reactions including rash, and sometimes also a high

temperature, increased levels of liver enzymes seen in blood tests, an increase in a type of white blood cell, and/or enlarged lymph nodes)
- joint pain
- muscle pain
- muscle wasting
- loss of appetite, or increase of appetite
- weight increase, or weight decrease
- high blood pressure
- chest pain
- feeling generally unwell (malaise)
- fever
- allergic reactions
- breast enlargement (in men)
- depression, disorientation, anxiety, insomnia, difficulty sleeping, and abnormal dream.
- elevated liver enzymes in the blood

Rare side effects (may affect up to 1 in 1,000 people)
- gait disturbance (abnormal manner of walking)
- swelling
- fast or irregular heart beat
- kidney pain
- widening of blood vessels
- severe or life threatening skin reaction including blisters (Stevens-Johnson syndrome).
- aching muscles, muscle tenderness of weakness, not caused by exercise
- enlargement of the liver and spleen

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- gallbladder disorders, including gall stones and infection
- diabetes mellitus and increased blood sugar levels
- irregular heart beat
- life threatening irregular heart beat
- immune reactivation syndrome (see section 2, Warnings and Precautions)

Side effects associated with combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and internal organs, breast enlargement and fatty lumps on the back of the neck ("buffalo hump"). The cause and long-term health effects of these conditions are not known. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, increased fats in the blood and resistance to insulin (insulin will not work as effectively).
In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your health care provider.

Furthermore, osteonecrosis (death of bone tissue) and immune reactivation syndrome have been reported in patients taking combination antiretroviral therapy (see section 2).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider as soon as possible.

5.How to store atazanavir (as sulfate) and ritonavir tablets

Keep this medicine out of the sight and reach of children.
Bottle pack
Do not store above 30°C. Store in the original package. Keep the bottle tightly closed.
Do not use this medicine after the expiry date which is stated on the bottle after {EXP}. The expiry date refers to the last day of that month.
Do not throw away any medicines via wastewater or household waste. Ask your health care provider how to throw away medicines you no longer use. These measures will help protect the environment.

6. Further Information

The active substances are: azatanavir sulfate and ritonavir. Each tablet contains atazanavir sulfate equivalent to 150 mg atazanavir and 50 mg ritonavir /300 mg atazanavir and 100 mg ritonavir.

The other ingredients are:
Core tablet:
Dicalcium phosphate anhydrous /Calcium hydrogen phosphate, colloidal silicon dioxide, copovidone, crospovidone, lactose monohydrate, magnesium stearate, sodium stearyl fumarate, sorbitan monolaurate, and Ferric oxide.

Film-coating:
Iron oxide yellow, Macrogol /PEG, Hypromellose and Titanium dioxide.

What Atazanavir (as sulfate) and Ritonavir tablets looks like and contents of the pack

Atazanavir (as sulfate) and Ritonavir tablets:

300 mg/100 mg: Yellow colored, oval shaped film coated tablets debossed with "L61" on one side and plain on other side.

300 mg/100 mg

30's Count: 85CC HDPE Bottle, 33 mm - 400 ARGUS CR Closure with TEKNIPLEX HS 123 induction sealing wad with silica gel canister 1g.

90's Count: 200CC HDPE Bottle, CAP 38 mm-400 ARGUS CR Closure with TEKNIPLEX HS 123 induction sealing wad with silica gel canister 2g.

Supplier and Manufacturer

Supplier:
Laurus Labs Limited,
2nd Floor, Serene Chambers, Road No.-7,
Banjara Hills, Hyderabad, Telangana – 500034,
India.

Manufacturer

Laurus Labs Limited, (Unit-2),
Plot No:19, 20 & 21, Western Sector, APSEZ,
Gurajapalem Village, Rambilli Mandal,
Anakapalli-District-531011,
Andhra Pradesh, India.

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