# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Atazanavir Krka 300 mg hard capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

Each hard capsule contains 158.86 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule (capsule)

*Atazanavir Krka 300 mg hard capsules*

Hard gelatine capsule, size no. 00. The body of the capsule is white or almost white colour, the cap of the capsule is dark brown colour. The capsule cap is imprinted with white mark A300. The content of the capsule is yellowish-white to yellow-white powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

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

## 4.2 Posology and method of administration

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

Posology

*Adults*

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

*Paediatric patients (6 years to less than 18 years of age and weighing at least 15 kg)*

The dose of atazanavir capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. Atazanavir Krka capsules must be taken with ritonavir and have to be taken with food.

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

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

[a] Ritonavir capsules, tablets or oral solution.

*Paediatric patients (at least 3 months of age and weighing at least 5 kg):*

Other formulations of this medicine may be available for paediatric patients at least 3 months of age and weighing at least 5 kg (see relevant Summary of Product Characteristics for alternative forms). Switching to capsules from other formulations is encouraged as soon as patients are able to consistently swallow capsules.

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

*Special populations*

*Renal impairment*

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

*Hepatic impairment*

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

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

*Pregnancy and Postpartum*

During the second and third trimesters of pregnancy:

Atazanavir Krka 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.

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

- If tenofovir disoproxil or an $H_2$-receptor antagonist is needed, a dose

increase to Atazanavir Krka 400 mg with ritonavir 100 mg with TDM may be considered (see sections 4.6 and 5.2).

- It is not recommended to use Atazanavir Krka with ritonavir for pregnant patients who are receiving both tenofovir disoproxil and an $H_2$-receptor antagonist.

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

During postpartum:

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

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

*Paediatric patients (less than 3 months of age)*

Atazanavir Krka should not be used in children less than 3 months because of safety concerns especially taking into account the potential risk of kernicterus.

Method of administration

For oral use. The capsules should be swallowed whole.

## 4.3 Contraindications

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

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

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

Combination of rifampicin (see section 4.5).

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

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

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

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

Co-administration with products containing St. John's wort (*Hypericum perforatum*) (see section 4.5).

## 4.4 Special warnings and precautions for use

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

<u>Patients with coexisting conditions</u>

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

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

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

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

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

Weight and metabolic parameters

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

In clinical studies, atazanavir (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators.

Hyperbilirubinaemia

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of 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 Krka may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it may result in a loss of therapeutic effect and development of resistance.

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

Withdrawal of ritonavir only under restrictive conditions

The recommended standard treatment is Atazanavir Krka boosted with ritonavir, ensuring optimal pharmacokinetic parameters and level of virologic suppression.

The withdrawal of ritonavir from the boosted regimen of Atazanavir Krka is not recommended, but may be considered in adults patients at the dose of 400 mg once daily with food only under the following combined restrictive conditions:

- absence of prior virologic failure
- undetectable viral load during the last 6 months under current regimen
- viral strains not harbouring HIV resistance associated mutations (RAMs) to current regimen.

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

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

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 may be considered.

Chronic kidney disease

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown an association between an increased incidence of chronic kidney disease and cumulative exposure to atazanavir/ritonavir-containing regimen in HIV-infected patients with an initially normal eGFR. This association was observed independently of exposure to tenofovir disoproxil. Regular monitoring of the renal function of patients should be maintained throughout the treatment duration (see section 4.8).

Nephrolithiasis

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

Immune reactivation syndrome

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

Osteonecrosis

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

Rash and associated syndromes

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

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. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. Atazanavir Krka should be discontinued if severe rash develops.

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

Interactions with other medicinal products

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

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

Atazanavir is metabolised principally by CYP3A4. Co-administration of Atazanavir Krka and medicinal products that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

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

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

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

Concomitant use of Atazanavir Krka /ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid

effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

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

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

Co-administration of Atazanavir Krka with proton pump inhibitors is not recommended (see section 4.5). If the combination of Atazanavir Krka with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of Atazanavir Krka 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 Krka with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate or norethindrone has not been studied, and therefore should be avoided (see section 4.5).

Paediatric population

*Safety*

Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8).

Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), Atazanavir Krka should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

*Efficacy*

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

Excipients

*Lactose*

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

*Other interactions*

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

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

**Table 2: Interactions between atazanavir and other medicinal products**

| **Medicinal products by therapeutic area** | **Interaction** | **Recommendations concerning co-administration** |
|---|---|---|
| **ANTI-HCV AGENTS** | | |
| **Grazoprevir 200 mg** | Atazanavir AUC ↑43% (↑30% | Co-administration of |

| | | |
|---|---|---|
| **once daily**<br>(atazanavir 300 mg/ ritonavir 100 mg once daily) | ↑57%)<br>Atazanavir $c_{max}$ ↑12% (↑1% ↑24%)<br>Atazanavir $c_{min}$ ↑23% (↑13% ↑134%)<br><br>Grazoprevir AUC: ↑958% (↑678% ↑1339%)<br>Grazoprevir $c_{max}$: ↑524% (↑342% ↑781%)<br>Grazoprevir $c_{min}$: ↑1064% (↑696% ↑1602%)<br><br>Grazoprevir concentrations were greatly increased when co-administered with atazanavir/ritonavir. | atazanavir and elbasvir/grazoprevir is contraindicated because of a significant increase in grazoprevir plasma concentrations and an associated potential increase in the risk of ALT elevations (see section 4.3). |
| **Elbasvir 50 mg once daily**<br>(atazanavir 300 mg/ ritonavir 100 mg once daily) | Atazanavir AUC ↑7% (↓2% ↑17%)<br>Atazanavir $c_{max}$ ↑2% (↓4% ↑8%)<br>Atazanavir $c_{min}$ ↑15% (↑2% ↑29%)<br><br>Elbasvir AUC: ↑376% (↑307% ↑456%)<br>Elbasvir $c_{max}$: ↑315% (↑246% ↑397%)<br>Elbasvir $c_{min}$: ↑545% (↑451% ↑654%)<br><br>Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir. | |
| **Sofosbuvir 400 mg / velpatasvir 100 mg /voxilaprevir 100 mg single dose***<br><br>(atazanavir 300 mg / ritonavir 100 mg once daily) | Sofosbuvir AUC : ↑40% (↑25% ↑57%)<br>Sofosbuvir $c_{max}$ :↑29% (↑9% ↑52%)<br>Velpatasvir AUC: ↑93% (↑58% ↑136%)<br>Velpatasvir $c_{max}$ : ↑29% (↑7% ↑56%)<br>Voxilaprevir AUC : ↑331% (↑276% ↑393%)<br>Voxilaprevir $c_{max}$ : ↑342% (↑265% ↑435%)<br>*Lack of pharmacokinetics interaction bounds 70-143%<br>Effect on atazanavir and ritonavir exposure has not been studied.<br>Expected:<br>↔ Atazanavir<br>↔ Ritonavir<br>The mechanism of interaction between atazanavir/ritonavir and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, Pgp, and CYP3A. | Co-administration of atazanavir with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Co-administration of atazanavir with voxilaprevir-containing regimens is not recommended. |
| **Glecaprevir 300 mg / pibrentasvir 120 mg once daily** | Glecaprevir AUC : ↑553% (↑424% ↑714%)<br>Glecaprevir $c_{max}$ : ↑306% (↑215% | Co-administration of atazanavir with glecaprevir/pibrentasvir |

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| (atazanavir 300 mg / ritonavir 100 mg once daily*) | ↑423%)<br>Glecaprevir $c_{min}$ : ↑1330% (↑885% ↑1970%)<br>Pibrentasvir AUC : ↑64% (↑48% ↑82%)<br>Pibrentasvir $c_{max}$ : ↑29% (↑15% ↑45%)<br>Pibrentasvir $c_{min}$: ↑129% (↑95% ↑168%)<br>* Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported. | is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3) |
| **ANTI-RETROVIRALS** | | |
| *Protease inhibitors:* The co-administration of atazanavir /ritonavir and other protease inhibitors has not been studied but would be expected to increase exposure to other protease inhibitors. Therefore, such co- administration is not recommended. | | |
| **Ritonavir 100 mg once daily** (atazanavir 300 mg once daily)<br><br>Studies conducted in HIV- infected patients. | Atazanavir AUC: ↑250% (↑144% ↑403%)*<br>Atazanavir $c_{max}$: ↑120% (↑56% ↑211%)*<br>Atazanavir $c_{min}$: ↑713% (↑359% ↑1339%)*<br><br>* In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28).<br>The mechanism of interaction between atazanavir and ritonavir is CYP3A4 inhibition. | Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics. |
| **Indinavir** | Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT. | Co-administration of atazanavir and indinavir is not recommended (see section 4.4). |
| *Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)* | | |
| **Lamivudine 150 mg twice daily + zidovudine 300 mg twice daily** (atazanavir 400 mg once daily) | No significant effect on lamivudine and zidovudine concentrations was observed. | Based on these data and because ritonavir is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of these medicinal products and atazanavir is not expected to significantly alter the exposure of the co-administered medicinal products. |
| **Abacavir** | The co-administration of abacavir and atazanavir is not expected to significantly alter the exposure of abacavir. | |
| **Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose** (atazanavir 400 mg single dose) | Atazanavir, simultaneous administration with ddI+d4T (fasted)<br>Atazanavir AUC ↓87% (↓92% ↓79%) | Didanosine should be taken at the fasted state 2 hours after atazanavir taken with food. The co-administration of |

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| | Atazanavir $c_{max}$ ↓89% (↓94% ↓82%)<br>Atazanavir $c_{min}$ ↓84% (↓90% ↓73%)<br><br>Atazanavir, dosed 1 hr after ddI+d4T (fasted)<br>Atazanavir AUC ↔3% (↓36% ↑67%)<br>Atazanavir $c_{max}$ ↑12% (↓33% ↑18%)<br>Atazanavir $c_{min}$ ↔3% (↓39% ↑73%)<br><br>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.<br>No significant effect on didanosine and stavudine concentrations was observed. | stavudine with atazanavir is not expected to significantly alter the exposure of stavudine. |
| **Didanosine (enteric coated capsules) 400 mg single dose** (atazanavir 300 mg once daily with ritonavir 100 mg once daily) | Didanosine (with food)<br>Didanosine AUC ↓34% (↓41% ↓27%) Didanosine $c_{max}$ ↓38% (↓48% ↓26%) Didanosine $c_{min}$ ↑25% (↓8% ↑69%)<br><br>No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations. | |
| **Tenofovir disoproxil fumarate 300 mg once daily** (atazanavir 300 mg once daily with ritonavir 100 mg once daily)<br><br>300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil<br><br>Studies conducted in HIV- infected patients | Atazanavir AUC ↓22% (↓35% ↓6%) *<br>Atazanavir $c_{max}$ ↓16% (↓30% ↔0%) *<br>Atazanavir $c_{min}$ ↓23% (↓43% ↑2%) *<br><br>* In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33).<br><br>The efficacy of atazanavir /ritonavir in combination with tenofovir disoproxil fumarate in treatment- experienced patients has been demonstrated in clinical | When co-administered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir disoproxil fumarate 300 mg (all as a single dose with food). |

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| | study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir disoproxil fumarate is unknown. | |
| **Tenofovir disoproxil fumarate 300 mg once daily** (atazanavir 300 mg once daily with ritonavir 100 mg once daily)<br><br>300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil. | Tenofovir disoproxil fumarate AUC ↑37% (↑30% ↑45%)<br>Tenofovir disoproxil fumarate $C_{max}$ ↑34% (↑20% ↑51%)<br>Tenofovir disoproxil fumarate $C_{min}$ ↑29% (↑21% ↑36%) | Patients should be closely monitored for tenofovir disoproxil fumarate-associated adverse reactions, including renal disorders. |
| *Non-nucleoside reverse transcriptase inhibitors (NNRTIs)* | | |
| **Efavirenz 600 mg once daily** (atazanavir 400 mg once daily with ritonavir 100 mg once daily) | Atazanavir (pm): all administered with food<br>Atazanavir AUC ↔0% (↓9% ↑10%)*<br>Atazanavir $c_{max}$ ↑17% (↑8% ↑27%)*<br>Atazanavir $c_{min}$ ↓42% (↓51% ↓31%)* | Co-administration of efavirenz and atazanavir is not recommended (see section 4.4) |
| **Efavirenz 600 mg once daily** (atazanavir 400 mg once daily with ritonavir 200 mg once daily) | Atazanavir (pm): all administered with food<br>Atazanavir AUC ↔6% (↓10% ↑26%) */**<br>Atazanavir $c_{max}$ ↔9% (↓5% ↑26%) */**<br>Atazanavir $c_{min}$ ↔12% (↓16% ↑49%) */**<br>* When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir $c_{min}$, might negatively impact the efficacy of atazanavir. The mechanism of efavirenz/atazanavir interaction is CYP3A4 induction.<br>** Based on historical comparison. | |
| **Nevirapine 200 mg twice daily** (atazanavir 400 mg once daily with ritonavir 100 mg once daily)<br><br>Study conducted in HIV infected patients | Nevirapine AUC ↑26% (↑17% ↑36%)<br>Nevirapine $c_{max}$ ↑21% (↑11% ↑32%)<br>Nevirapine $c_{min}$ ↑35% (↑25% ↑47%)<br><br>Atazanavir AUC ↓19% (↓35% ↑2%) *<br>Atazanavir $c_{max}$ ↔2% (↓15% ↑24%) *<br>Atazanavir $c_{min}$ ↓59% (↓73% | Co-administration of nevirapine and atazanavir is not recommended (see section 4.4) |

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| | ↓40%) *<br><br>* When compared to atazanavir 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir $C_{min}$, might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir interaction is CYP3A4 induction. | |
| *Integrase Inhibitors* | | |
| **Raltegravir 400 mg twice daily**<br>(atazanavir/ritonavir) | Raltegravir AUC ↑41%<br>Raltegravir $c_{max}$ ↑24%<br>Raltegravir $c_{12hr}$ ↑77%<br><br>The mechanism is UGT1A1 inhibition. | No dose adjustment required for raltegravir. |
| **ANTIBIOTICS** | | |
| **Clarithromycin 500 mg twice daily**<br>(atazanavir 400 mg once daily) | Clarithromycin AUC ↑94% (↑75% ↑116%)<br>Clarithromycin $c_{max}$ ↑50% (↑32% ↑71%)<br>Clarithromycin $c_{min}$ ↑160% (↑135% ↑188%)<br><br>14-OH clarithromycin<br>14-OH clarithromycin AUC ↓70% (↓74% ↓66%)<br>14-OH clarithromycin $c_{max}$ ↓72% (↓76% ↓67%)<br>14-OH clarithromycin $c_{min}$ ↓62% (↓66% ↓58%)<br><br>Atazanavir AUC ↑28% (↑16% ↑43%)<br>Atazanavir $c_{max}$ ↔6% (↓7% ↑20%)<br>Atazanavir $c_{min}$ ↑91% (↑66% ↑121%)<br><br>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 is co-administered with clarithromycin. |
| **ANTIFUNGALS** | | |
| **Ketoconazole 200 mg once daily**<br>(atazanavir 400 mg once daily) | No significant effect on atazanavir concentrations was observed. | Ketoconazole and itraconazole should be used cautiously with atazanavir /ritonavir, 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, | |

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| | where ketoconazole AUC showed a 3-fold increase, atazanavir /ritonavir is expected to increase ketoconazole or itraconazole concentrations. | |
| **Voriconazole 200 mg twice daily** (atazanavir 300 mg/ritonavir 100 mg once daily)<br><br>Subjects with at least one functional CYP2C19 allele. | Voriconazole AUC ↓33% (↓42% ↓22%)<br>Voriconazole $c_{max}$ ↓10% (↓22% ↓4%)<br>Voriconazole $c_{min}$ ↓39% (↓49% ↓28%)<br><br>Atazanavir AUC ↓12% (↓18% ↓5%<br>Atazanavir $c_{max}$ ↓13% (↓20% ↓4%)<br>Atazanavir $c_{min}$ ↓ 20 % (↓28% ↓10%)<br><br>Ritonavir AUC ↓12% (↓17% ↓7%)<br>Ritonavir $c_{max}$ ↓9% (↓17% ↔0%)<br>Ritonavir $c_{min}$ ↓25% (↓35% ↓14%)<br><br>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 with ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see section 4.4).<br><br>At the time voriconazole treatment is required, a patient's CYP2C19 genotype should be performed if feasible.<br><br>Therefore if the combination is unavoidable, the following recomendations are made according to the CYP2C19 status:<br><br>- 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.<br><br>- in patients without a functional CYP2C19 allele, close clinical and laboratory monitoring of voriconazole-associated adverse events is recommended.<br><br>If genotyping is not feasible, full monitoring of safety and efficacy should be performed. |
| **Voriconazole 50 mg twice daily** (atazanavir 300 mg/ritonavir 100 mg once daily)<br><br>Subjects without a functional CYP2C19 allele. | Voriconazole AUC ↑561% (↑451% ↑699%)<br>Voriconazole $c_{max}$ ↑438% (↑355% ↑539%)<br>Voriconazole $c_{min}$ ↑765% (↑571% ↑1,020%)<br><br>Atazanavir AUC ↓20% (↓35% ↓3%)<br>Atazanavir $c_{max}$ ↓19% (↓34% ↔0.2%)<br>Atazanavir $c_{min}$ ↓ 31 % (↓46 % ↓13%)<br><br>Ritonavir AUC ↓11% (↓20% ↓1%)<br>Ritonavir $c_{max}$ ↓11% (↓24% ↑4%)<br>Ritonavir $c_{min}$ ↓19% (↓35% ↑1%)<br><br>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 /ritonavir was co-administered with fluconazole. | No dosage adjustments are needed for fluconazole and atazanavir. |

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| **ANTIMYCOBACTERIAL** | | |
| **Rifabutin 150 mg twice weekly**<br>(atazanavir 300 mg and ritonavir 100 mg once daily) | Rifabutin AUC ↑48% (↑19% ↑84%) **<br>Rifabutin $c_{max}$ ↑149% (↑103% ↑206%) **<br>Rifabutin $c_{min}$ ↑40% (↑5% ↑87%) **<br><br>25-O-desacetyl-rifabutin AUC ↑990% (↑714% ↑1361%) **<br>25-O-desacetyl-rifabutin $c_{max}$ ↑677% (↑513% ↑883%) **<br>25-O-desacetyl-rifabutin $c_{min}$ ↑1045% (↑715% ↑1510%) **<br><br>** When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC ↑119% (↑78% ↑169%).<br><br>In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin. | When given with atazanavir, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for atazanavir. |
| **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 or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen. | The combination of rifampicin and atazanavir is contraindicated (see section 4.3). |
| **ANTIPSYCHOTICS** | | |
| **Quetiapine** | Due to CYP3A4 inhibition by atazanavir, concentrations of quetiapine are expected to increase. | Co-administration of quetiapine with atazanavir is contraindicated as atazanavir may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see section 4.3). |
| **Lurasidone** | Atazanavir is expected to increase | Co-administration of |

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| | plasma levels of lurasidone due to CYP3A4 inhibition. | lurasidone with atazanavir is contraindicated as this may increase lurasidone-related toxicity (see section 4.3). |
| **ACID REDUCING AGENTS** | | |
| *$H_2$-Receptor antagonists* | | |
| **Without Tenofovir disoproxil** | | |
| In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily | | **For patients not taking tenofovir disoproxil,** if atazanavir 300 mg/ritonavir 100 mg and $H_2$-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg twice daily should not be exceeded. If a higher dose of an $H_2$-receptor antagonist is required (e.g., famotidine 40 mg twice daily or equivalent) an increase of the atazanavir /ritonavir dose from 300/100 mg to 400/100 mg can be considered. |
| **Famotidine 20 mg twice daily** | Atazanavir AUC ↓18% (↓25% ↑1%)<br>Atazanavir $c_{max}$ ↓20% (↓32% ↓7%)<br>Atazanavir $c_{min}$ ↔1% (↓16% ↑18%) | |
| **Famotidine 40 mg twice daily** | Atazanavir AUC ↓23% (↓32% ↓14%)<br>Atazanavir $c_{max}$ ↓23% (↓33% ↓12%)<br>Atazanavir $c_{min}$ ↓20% (↓31% ↓8%) | |
| In Healthy volunteers with atazanavir/ritonavir at an increased dose of 400/100 mg once daily | | |
| **Famotidine 40 mg twice daily** | Atazanavir AUC ↔3% (↓14% ↑22%)<br>Atazanavir $c_{max}$ ↔2% (↓13% ↑8%)<br>Atazanavir $c_{min}$ ↓14% (↓32% ↑8%) | |
| **With Tenofovir disoproxil fumarate 300 mg once daily (equivalent to 245 mg tenofovir disoproxil)** | | |
| In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg once daily | | **For patients who are taking tenofovir disoproxil,** if atazanavir/ritonavir with both tenofovir disoproxil and an $H_2$-receptor antagonist are co-administered, a dose increase of atazanavir to 400 mg with 100 mg of ritonavir is recommended. A dose equivalent to famotidine 40 mg twice daily should not be exceeded. |
| **Famotidine 20 mg twice daily** | Atazanavir AUC ↓21% (↓34% ↓4%)*<br>Atazanavir $c_{max}$ ↓21% (↓36% ↓4%)*<br>Atazanavir $c_{min}$ ↓19% (↓37% ↑5%)* | |
| **Famotidine 40 mg twice daily** | Atazanavir AUC ↓24% (↓36% ↓11%)*<br>Atazanavir $c_{max}$ ↓23% (↓36% ↓8%)*<br>Atazanavir $c_{min}$ ↓25% (↓47% ↑7%)* | |
| In HIV-infected patients with atazanavir/ritonavir at an increased dose of 400/100 mg once daily | | |
| **Famotidine 20 mg twice daily** | Atazanavir AUC ↑18% (↑6.5% ↑30%)*<br>Atazanavir $c_{max}$ ↑18% (↑6.7% ↑31%)*<br>Atazanavir $c_{min}$ ↑24 % (↑10% ↑39%)* | |

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| **Famotidine 40 mg twice daily** | Atazanavir AUC ↔2.3% (↓13% ↑10%)*<br>Atazanavir $c_{max}$ ↔5% (↓17% ↑8.4%)*<br>Atazanavir $c_{min}$↔1.3% (↓10% ↑15)* | |
| | * When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg *without tenofovir disoproxil*, atazanavir concentrations are expected to be additionally decreased by about 20%.<br><br>The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with $H_2$- blockers. | |
| *Proton pump inhibitors* | | |
| **Omeprazole 40 mg once daily** (atazanavir 400 mg once daily with ritonavir 100 mg once daily) | Atazanavir (am): 2 hr after omeprazole<br>Atazanavir AUC ↓61% (↓65% ↓55%)<br>Atazanavir $c_{max}$ ↓66% (↓62% ↓49%)<br>Atazanavir $c_{min}$ ↓65% (↓71% ↓59%) | Co-administration of atazanavir with ritonavir and proton pump inhibitors is not recommended. If the combination is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded (see section 4.4). |
| **Omeprazole 20 mg once daily** (atazanavir 400 mg once daily with ritonavir 100 mg once daily) | Atazanavir (am): 1 hr after omeprazole<br>Atazanavir AUC ↓30% (↓43% ↓14%)*<br>Atazanavir $c_{max}$ ↓31% (↓42% ↓17%)*<br>Atazanavir $c_{min}$ ↓31% (↓46% ↓12%)*<br><br>* When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily.<br>The decrease in AUC, $c_{max}$, and $c_{min}$ was not mitigated when an increased dose of atazanavir /ritonavir (400/100 mg once daily) was temporally separated from omeprazole by 12 hours. Although not studied, similar results are expected with other proton pump inhibitors. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors. | |

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| *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. | Atazanavir 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 and/or ritonavir. | Co-administration of alfuzosin with atazanavir is contraindicated (see section 4.3) |
| **ANTICOAGULANTS** | | |
| *Direct-acting oral anticoagulants (DOACs)* | | |
| **Apixaban**<br><br>**Rivaroxaban** | Potential for increased apixaban and rivaroxaban concentrations which can result in a higher risk of bleeding.<br>The mechanism of interaction is inhibition of CYP3A4 ≠ and P-gp by atazanavir/ritonavir.<br><br>Ritonavir is a strong inhibitor of both CYP3A4 and P-gp.<br><br>Atazanavir is an inhibitor of CYP3A4. The potential inhibition of P-gp by atazanavir is unknown and cannot be excluded. | Co-administration of apixaban or rivaroxaban and atazanavir with ritonavir is not recommended |
| **Dabigatran** | Potential for increased dabigatran concentrations which can result in a higher risk of bleeding. The mechanism of interaction is P-gp inhibition.<br><br>Ritonavir is a strong P-gp inhibitor.<br><br>Potential P-gp inhibition by atazanavir is unknown and cannot be excluded. | Co-administration of dabigatran and atazanavir with ritonavir is not recommended. |
| **Edoxaban** | Potential for increased edoxaban concentrations which can result in a higher risk of bleeding. The mechanism of interaction is P-gp inhibition by atazanavir /ritonavir.<br><br>Ritonavir is a strong P-gp inhibitor.<br><br>Potential P-gp inhibition by atazanavir is unknown and cannot be excluded. | Exercise caution when edoxaban is used with atazanavir.<br><br>Please refer to edoxaban SmPC section 4.2 and 4.5 for appropriate edoxaban dosage recommendations for co-administration with P-gp inhibitors. |
| *Vitamin K antagonists* | | |
| **Warfarin** | Co-administration with atazanavir has the potential to increase or decrease warfarin concentrations. | It is recommended that the International Normalised Ratio (INR) be monitored |

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| | | carefully during treatment with atazanavir, especially when commencing therapy. |
| **ANTIEPILEPTICS** | | |
| **Carbamazepine** | Atazanavir may increase plasma levels of carbamazepine due to CYP3A4 inhibition.<br>Due to carbamazepine inducing effect, a reduction in atazanavir exposure cannot be ruled out. | Carbamazepine should be used with caution in combination with atazanavir. If necessary, monitor carbamazepine serum concentrations and adjust the dose accordingly. Close monitoring of the patient's virologic response should be excercised. |
| **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 exposure cannot be ruled out. | Phenobarbital and phenytoin should be used with caution in combination with atazanavir /ritonavir.<br><br>When atazanavir/ritonavir is co-administered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required.<br><br>Close monitoring of patient's virologic response should be exercised. |
| **Lamotrigine** | Co-administration of lamotrigine and atazanavir /ritonavir may decrease lamotrigine plasma concentrations due to UGT1A4 induction. | Lamotrigine should be used with caution in combination with atazanavir /ritonavir.<br><br>If necessary, monitor lamotrigine concentrations and adjust the dose accordingly. |
| **ANTINEOPLASTICS AND IMMUNOSUPRESSANTS** | | |
| *Antineoplastics* | | |
| **Irinotecan** | Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. | If atazanavir is co-administered with irinotecan, patients should be closely monitored for adverse events related to irinotecan. |
| *Immunosuppressants* | | |
| **Cyclosporin**<br>**Tacrolimus** | Concentrations of these immunosuppressants may be | More frequent therapeutic |

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| **Sirolimus** | increased when co-administered with atazanavir due to CYP3A4 inhibition. | concentration monitoring of these medicinal products is recommended until plasma levels have been stabilised. |
| **CARDIOVASCULAR AGENTS** | | |
| *Antiarrhythmics* | | |
| **Amiodarone,**<br>**Systemic lidocaine,**<br>**Quinidine** | Concentrations of these antiarrhythmics may be increased when co-administered with atazanavir. 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. | Caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of quinidine is contraindicated (see section 4.3). |
| *Calcium channel blockers* | | |
| **Bepridil** | Atazanavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index. | Co-administration with bepridil is contraindicated (see section 4.3) |
| **Diltiazem 180 mg once daily**<br>(atazanavir 400 mg<br>once daily) | Diltiazem AUC ↑125% (↑109% ↑141%)<br>Diltiazem $c_{max}$ ↑98% (↑78% ↑119%)<br>Diltiazem $c_{min}$ ↑142% (↑114% ↑173%)<br><br>Desacetyl-diltiazem AUC ↑165% (↑145% ↑187%)<br>Desacetyl-diltiazem $c_{max}$ ↑172% (↑144% ↑203%)<br>Desacetyl-diltiazem $c_{min}$ ↑121% (↑102% ↑142%)<br><br>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 /ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition. | An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. |
| **Verapamil** | Serum concentrations of verapamil may be increased by atazanavir due to CYP3A4 inhibition. | Caution should be exercised when verapamil is co-administered with atazanavir. |
| **CORTICOSTEROIDS** | | |
| **Fluticasone propionate intranasal 50 µg 4 times daily for 7 days**<br>(ritonavir 100 mg capsules | The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% | Co-administration of atazanavir/ritonavir and these glucocorticoids is not recommended |

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| twice daily) | (90% confidence interval 82%-89%). Greater effects may be expected when fluticasone propionate is inhaled.<br>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. | 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 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 (see section 4.4). Also see PULMONARY ARTERIAL HYPERTENSION in this table for futher information regarding co- administration of atazanavir with sildenafil. |
| **HERBAL PRODUCTS** | | |
| **St. John's wort (Hypericum perforatum)** | Concomitant use of St. John's wort with atazanavir 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 with products containing St. John's wort is contraindicated. |
| **HORMONAL CONTRACEPTIVES** | | |
| **Ethinyloestradiol 25 µg + norgestimate**<br>(atazanavir 300 mg once daily with ritonavir 100 mg once daily) | Ethinyloestradiol AUC ↓19% (↓25% ↓13%)<br>Ethinyloestradiol $c_{max}$ ↓16% (↓26% ↓5%)<br>Ethinyloestradiol $c_{min}$ ↓37% (↓45% ↓29%)<br><br>Norgestimate AUC ↑85% (↑67% ↑105%) | If an oral contraceptive is administered with atazanavir/ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinyloestradiol and that the patient be reminded of strict |

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| | Norgestimate $c_{max}$ ↑68% (↑51% ↑88%)<br>Norgestimate $c_{min}$ ↑102% (↑77% ↑131%)<br><br>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.<br><br>The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance. | compliance with this contraceptive dosing regimen. Co-administration of atazanavir /ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended. |
| **Ethinyloestradiol 35 µg + norethindrone**<br>(atazanavir 400 mg once daily) | Ethinyloestradiol AUC ↑48% (↑31% ↑68%)<br>Ethinyloestradiol $c_{max}$ ↑15% (↓1% ↑32%)<br>Ethinyloestradiol $c_{min}$ ↑91% (↑57% ↑133%)<br><br>Norethindrone AUC ↑110% (↑68% ↑162%)<br>Norethindrone $c_{max}$ ↑67% (↑42% ↑196%)<br>Norethindrone $c_{min}$ ↑262% (↑157% ↑409%)<br><br>The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance. | |
| **LIPID MODIFYING AGENTS** | | |
| *HMG-CoA reductase inhibitors* | | |
| **Simvastatin**<br>**Lovastatin** | Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with atazanavir may result in increased concentrations. | Co-administration of simvastatin or lovastatin with atazanavir 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 is not recommended. If the use of atorvastatin is considered strictly |

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| | | necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring (see section 4.4). |
| **Pravastatin**<br>**Fluvastatin** | Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co- administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9. | Caution should be exercised. |
| *Other lipid-modifying agents* | | |
| **Lomitapide** | Lomitapide is highly dependent on CYP3A4 for metabolism and co-administration with atazanavir with ritonavir may result in increased concentrations. | Co-administration of lomitapide and atazanavir with ritonavir is contraindicated due to a potential risk of markedly increased transaminase levels and hepatotoxicity (see section 4.3). |
| **INHALED BETA AGONISTS** | | |
| **Salmeterol** | Co-administration with atazanavir may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events.<br><br>The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir. | Co-administration of salmeterol with atazanavir is not recommended (see section 4.4). |
| **OPIOIDS** | | |
| **Buprenorphine, once daily, stable maintenance dose**<br>(atazanavir 300 mg once daily with ritonavir 100 mg once daily) | Buprenorphine AUC ↑67%<br>Buprenorphine $c_{max}$ ↑37%<br>Buprenorphine $c_{min}$ ↑69%<br><br>Norbuprenorphine AUC ↑105%<br>Norbuprenorphine $c_{max}$ ↑61%<br>Norbuprenorphine $c_{min}$ ↑101%<br><br>The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir (when given with ritonavir) were not significantly affected. | Co-administration with atazanavir with ritonavir warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. |
| **Methadone, stable maintenance dose**<br>(atazanavir 400 mg once daily) | No significant effect on methadone concentrations was observed. Given that low dose ritonavir (100 mg twice daily) has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co- administered with atazanavir, based on these | No dosage adjustment is necessary if methadone is co-administered with atazanavir. |

| | | |
|---|---|---|
| | data. | |
| **PULMONARY ARTERIAL HYPERTENSION** | | |
| *PDE5 Inhibitors* | | |
| **Sildenafil** | Co-administration with atazanavir may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-inhibitor-associated adverse events.<br><br>The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir. | A safe and effective dose in combination with atazanavir has not been established for sildenafil when used to treat pulmonary arterial hypertension. Sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated (see section 4.3). |
| **SEDATIVES** | | |
| *Benzodiazepines* | | |
| **Midazolam**<br>**Triazolam** | Midazolam and triazolam are extensively metabolised by CYP3A4. Co-administration with atazanavir may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of atazanavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels. | Co-administration of atazanavir with triazolam or orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co- administration of atazanavir and parenteral midazolam. If atazanavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. |

*In case of withdrawal of ritonavir from the recommended atazanavir boosted regimen (see section 4.4)*

The same recommendations for drug interactions would apply except:

- that co-administration is not recommended with tenofovir, carbamazepine, phenytoin, phenobarbital, proton pump inhibitors, and buprenorphine.
- that co-administration with famotidine is not recommended but if required, atazanavir without ritonavir should be administered either 2 hours after

famotidine or 12 hours before. No single dose of famotidine should exceed 20 mg, and the total daily dose of famotidine should not exceed 40 mg.

- the need to consider that
  - co-administration of apixaban, dabigatran, or rivaroxaban and atazanavir without ritonavir may affect apixaban, dabigatran, or rivaroxaban concentrations
  - co-administration of voriconazole and atazanavir without ritonavir may affect atazanavir concentrations
  - co-administration of fluticasone and atazanavir without ritonavir may increase fluticasone concentrations relative to fluticasone given alone
  - if an oral contraceptive is administered with atazanavir without ritonavir, it is recommended that the oral contraceptive contain no more than 30 µg of ethinyloestradiol
  - no dose adjustment of lamotrigine is required

*Paediatric population*

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data in pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative toxicity of atazanavir. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of Atazanavir Krka with ritonavir may be considered during pregnancy only if the potential benefit justifies the potential risk.

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

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

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

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

Breast-feeding

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

Fertility

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Summary of the safety profile

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

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

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

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during postmarketing surveillance. A large prospective observational study has shown an association between an increased incidence of chronic kidney disease and cumulative exposure to atazanavir/ritonavir-containing regimen in HIV-infected patients with an initially normal eGFR. This association was observed independently of exposure to tenofovir disoproxil. Regular monitoring of the renal function of patients should be maintained throughout the treatment duration (see section 4.4).

Tabulated list of adverse reactions

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

| | |
|---|---|
| *Immune system disorders:* | uncommon: hypersensitivity |
| *Metabolism and nutrition disorders* | uncommon: weight decreased, weight gain, anorexia, appetite increased |
| *Psychiatric disorders:* | uncommon: depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream |
| *Nervous system disorders:* | common: headache;<br>uncommon: peripheral neuropathy, syncope, amnesia, dizziness, somnolence, dysgeusia |
| *Eye disorders:* | common: ocular icterus |
| *Cardiac disorders:* | uncommon: torsades de pointes[a]<br>rare: QTc prolongation[a], oedema, palpitation |
| *Vascular disorders:* | uncommon: hypertension |
| *Respiratory, thoracic and mmediastinal disorders* | uncommon: dyspnoea |
| *Gastrointestinal disorders:* | common: vomiting, diarrhoea, abdominal pain, nausea, dyspepsia;<br>uncommon: pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth |
| *Hepatobiliary disorders:* | common: jaundice;<br>uncommon: hepatitis, cholelithiasis[a], cholestasis[a];<br>rare: hepatosplenomegaly, cholecystitis[a] |

| | |
|---|---|
| *Skin and subcutaneous tissue disorders:* | common: rash;<br>uncommon: erythemia multiforme[a,b], toxic skin eruptions[a,b], drug rash with eosinophilia and systemic symptoms (DRESS) syndrome[a,b], angioedema[a], urticaria, alopecia, pruritus;<br>rare: Stevens-Johnson syndrome[a,b], vesiculobullous rash, eczema, vasodilatation |
| *Musculoskeletal and connective tissue disorders* | uncommon: muscle atrophy, arthralgia, myalgia;<br>*rare:* myopathy |
| *Renal and urinary disorders:* | uncommon: nephrolithiasis[a], haematuria, proteinuria, pollakiuria, interstitial nephritis; chronic kidney disease[a]<br>rare: kidney pain |
| *Reproductive system and breast disorders:* | uncommon: gynaecomastia |
| *General disorders and administration site conditions:* | common: fatigue;<br>uncommon: chest pain, malaise, pyrexia, asthenia;<br>rare: gait disturbance |

[a]These adverse reactions were identified through post-marketing surveillance, however, the frequencies were estimated from a statistical calculation based on the total number of patients exposed to atazanavir in randomised controlled and other available clinical trials (n = 2321).

[b]See description of selected adverse reactions for more details.

Description of selected adverse reactions

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

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

Metabolic parameters

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

Rash and associated syndromes

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

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

*Laboratory abnormalities*

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

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2% of patients receiving regimens containing 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 and Grade 3-4 total bilirubin elevations.

Paediatric population

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

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

Other special populations

*Patients co-infected with hepatitis B and/or hepatitis C virus*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 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).

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

## 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

**Resistance**

*Antiretroviral treatment 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 boosted atazanavir, the I50L substitution did not emerge in any patient without baseline PI substitutions. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir (with or without ritonavir). While it may contribute to decreased susceptibility to atazanavir when it occurs with other protease substitutions, in clinical studies N88S by itself does not always lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy.

**Table 3. De novo substitutions in treatment naive patients failing therapy with atazanavir + ritonavir (Study 138, 96 weeks)**

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

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

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

*Antiretroviral treatment experienced adult patients*

In antiretroviral treatment experienced patients from Studies 009, 043, and 045, 100 isolates from patients designated as virological failures on therapy that

included either atazanavir, atazanavir + ritonavir, or atazanavir + saquinavir were determined to have developed resistance to atazanavir. Of the 60 isolates from patients treated with either atazanavir or atazanavir + ritonavir, 18 (30%) displayed the I50L phenotype previously described in naive patients.

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

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

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

[b] Ten patients had baseline phenotypic resistance to atazanavir + ritonavir (fold change [FC]>5.2). FC susceptibility in cell culture relative to the wild-type reference was assayed using PhenoSense™ (Monogram Biosciences, South San Francisco, California, USA)

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

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

## Clinical results

*In antiretroviral naive adult patients*

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

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

**Table 5: Efficacy Outcomes in Study 138[a]**

| | atazanavir /ritonavir[b] (300 mg/100 mg once daily) n=440 | | Lopinavir/ritonavir[c] (400 mg/100 mg twice daily) n=443 | |
|---|---|---|---|---|
| | **Week 48** | **Week 96** | **Week 48** | **Week 96** |
| **HIV RNA <50 copies/ml, %** | | | | |
| All patients[d] | 78 | 74 | 76 | 68 |
| Difference estimate [95% CI][d] | Week 48: 1.7% [-3.8%, 7.1%]<br>Week 96: 6.1% [0.3%, 12.0%] | | | |
| Per protocol analysis[e] | 86 (n=392[f]) | 91 (n=352) | 89 (n=372) | 89 (n=331) |

| | | | | |
|---|---|---|---|---|
| Difference estimate[e] [95% CI] | Week 48: -3% [-7.6%, 1.5%]<br>Week 96: 2.2% [-2.3%, 6.7%] | | | |
| HIV RNA <50 copies/ml, % by Baseline Characteristic[d] | | | | |
| HIV RNA <100,000 copies/ml | 82 (n=217) | 75 (n=217) | 81 (n=218) | 70 (n=218) |
| ≥100,000 copies/ml | 74 (n=223) | 74 (n=223) | 72 (n=225) | 66 (n=225) |
| CD4 count <50 cells/$mm^3$ | 78 (n=58) | 78 (n=58) | 63 (n=48) | 58 (n=48) |
| 50 to <100 cells/$mm^3$ | 76 (n=45) | 71 (n=45) | 69 (n=29) | 69 (n=29) |
| 100 to <200 cells/$mm^3$ | 75 (n=106) | 71 (n=106) | 78 (n=134) | 70 (n=134) |
| ≥ 200 cells/$mm^3$ | 80 (n=222) | 76 (n=222) | 80 (n=228) | 69 (n=228) |
| **HIV RNA Mean Change from Baseline, $log_{10}$ copies/ml** | | | | |
| All patients | -3.09 (n=397) | -3.21 (n=360) | -3.13 (n=379) | -3.19 (n=340) |
| **CD4 Mean Change from Baseline, cells/$mm^3$** | | | | |
| All patients | 203 (n=370) | 268 (n=336) | 219 (n=363) | 290 (n=317) |
| CD4 Mean Change from Baseline, cells/$mm^3$ by Baseline Characteristic | | | | |
| HIV RNA <100,000 copies/ml | 179 (n=183) | 243 (n=163) | 194 (n=183) | 267 (n=152) |
| ≥100,000 copies/ml | 227 (n=187) | 291 (n=173) | 245 (n=180) | 310 (n=165) |

[a] Mean baseline CD4 cell count was 214 cells/$mm^3$ (range 2 to 810 cells/$mm^3$) and mean baseline plasma HIV-1 RNA was

4.94 $log_{10}$ copies/ml (range 2.6 to 5.88 $log_{10}$ copies/ml)

[b] atazanavir /RTV with tenofovir disoproxil fumarate/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

[c] Lopinavir/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

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

[e] Per protocol analysis: Excluding non-completers and patients with major protocol deviations.

[f] Number of patients evaluable.

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

*Study 136 (INDUMA)*

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

Eleven subjects (13%) in the unboosted atazanavir group and 6 (7%) in the

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

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

*In antiretroviral experienced adult patients*

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

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

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

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

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥ 4 | 27 (12/45) | 24 (11/45) | 28 (14/50) | 20 (10/49) | NA | NA |
| **CD4 Mean Change from Baseline, cells/mm$^3$** | | | | | | |
| All patients | 110 (n=83) | 122 (n=60) | 121 (n=94) | 154 (n=60) | NA | NA |

[a] The mean baseline CD4 cell count was 337 cells/mm$^3$ (range: 14 to 1,543 cells/mm$^3$) and the mean baseline plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/ml (range: 2.6 to 5.88 $\log_{10}$ copies/ml).

[b] ATV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

[c] LPV/RTV with tenofovir disoproxil fumarate/emtricitabine (fixed dose 300 mg/200 mg tablets once daily).

[d] Confidence interval.

[e] Number of patients evaluable.

[f] Intent-to-treat analysis, with missing values considered as failures. Responders on LPV/RTV who completed treatment before Week 96 are excluded from Week 96 analysis. The proportion of patients with HIV RNA < 400 copies/ml were 53% and 43% for ATV/RTV and 54% and 46% for LPV/RTV at weeks 48 and 96 respectively.

[g] Select substitutions include any change at positions L10, K20, L24, V32, L33, M36, M46, G48, I50, I54, L63, A71, G73, V82, I84, and L90 (0-2, 3, 4 or more) at baseline.

NA = not applicable.

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

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

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

*Paediatric population*

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

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

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

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

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

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

[b] Number of patients evaluable.

[c] PI major L24I, D30N, V32I, L33F, M46IL, I47AV, G48V, I50LV, F53LY, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M; PI minor: L10CFIRV, V11I, E35G, K43T, Q58E, A71ILTV, G73ACST, T74P, N83D, L89V.

[d] Includes patients with baseline resistance data.

NA = not applicable.

## 5.2 Pharmacokinetic properties

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

*Absorption:* in HIV-infected patients (n=33, combined studies), multiple dosing

of atazanavir 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, $c_{max}$ of 4466 (42%) ng/ml, with time to $c_{max}$ of approximately 2.5 hours. The geometric mean (CV%) for atazanavir $c_{min}$ and AUC was 654 (76%) ng/ml and 44185 (51%) ng•h/ml, respectively.

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

Food effect: co-administration of 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 $^{14}$C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected

adult patients (n=33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal.

Special populations

*Renal impairment*: in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for 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-∞) was 42% greater in subjects with impaired hepatic function than in healthy subjects. The mean half-life of atazanavir in hepatically impaired subjects was 12.1 hours compared to 6.4 hours in healthy subjects. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

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

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

*Pregnancy:*

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

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

| | **atazanavir 300 mg with ritonavir 100 mg** |
|---|---|

| **Pharmacokinetic Parameter** | **2nd Trimester** (n=9) | **3rd Trimester** (n=20) | **postpartum**[a] (n=36) |
|---|---|---|---|
| $C_{max}$ ng/mL Geometric mean (CV%) | 3729.09 (39) | 3291.46 (48) | 5649.10 (31) |
| AUC ng•h/mL Geometric mean (CV%) | 34399.1 (37) | 34251.5 (43) | 60532.7 (33) |
| $C_{min}$ ng/mL[b] Geometric mean (CV%) | 663.78 (36) | 668.48 (50) | 1420.64 (47) |

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

[b] Cmin is concentration 24 hours post-dose

*Paediatric population*

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

## 5.3 Preclinical safety data

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

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

prolongation should be considered in cases of overdose (see section 4.9).

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

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic activation. In *in vivo* studies in rats, atazanavir did not induce micronuclei in bone marrow, DNA damage in duodenum (comet assay), or unscheduled DNA repair in liver at plasma and tissue concentrations exceeding those that were clastogenic *in vitro*.

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

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Capsule contents

lactose monohydrate

crospovidone (type A)

magnesium stearate

Capsule shell

*Body:*

titanium dioxide (E171)
gelatine

*Cap:*
titanium dioxide (E171)
yellow ferric oxide (E172)
red ferric oxide (E172)
black ferric oxide (E172)
gelatine
ink:
shellac
titanium dioxide (E171)
potassium hydroxide

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

Shelf life after first opening is 2 months, stored below 25°C.

## 6.4 Special precautions for storage

Store below 30°C.
Keep the container tightly closed in order to protect from moisture.

## 6.5 Nature and contents of container

HDPE tablet container with child-resistant tamper evident PP with desiccant closure: 30 hard capsules and 90 (3 x 30) hard capsules, in a box.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

## 8 MARKETING AUTHORISATION NUMBER(S)

PLGB 01656/0289

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

## 10 DATE OF REVISION OF THE TEXT

22/07/2023