Summary characteristics for pharmaceutical products

1.Name of the medicinal product

[HA749 trade name]†

2.Qualitative and quantitative composition

Each film-coated tablet contains 300 mg atazanavir (as sulfate) and 100 mg ritonavir.
Each film-coated tablet contains about 142 mg of lactose monohydrate.
For the full list of excipients, see section 6.1

3.Pharmaceutical form

Film-coated tablet.
Pale yellow to yellow colored, capsule shaped, biconvex, film coated tablet debossed with 'D09' on one side and plain surface on the other side.

4.Clinical particulars

4.1 Therapeutic Indications

[HA749 trade name] is indicated for the treatment of HIV-1 infected adults and children weighing at least 25 kg, in combination with other antiretroviral medicinal products.
The choice of fixed dose combination [HA749 trade name] for use in treatment-experienced patients should be based on treatment history of patients and, if available, also on individual viral resistance testing (see sections 4.4 and 5.1).
Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.
[HA749 trade name] may be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by WHO, should be consulted.

4.2 Posology and method of adminstration

[HA749 trade name] should be prescribed by health care providers who are experienced in the treatment of HIV infection.

Posology

Adults and children weighing at least 25 kg

The recommended dose of [HA749 trade name] is one tablet (atazanavir/ritonavir 300 mg/100 mg), taken once daily with food.

Special populations

Paediatric patients

For *children 3 months and older weighing at least 10 kg*, other pharmaceutical forms/strengths containing lower amounts of atazanavir and/or ritonavir should be administered.

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

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† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Hepatic impairment

[HA749 trade name] should be used with caution in patients with mild hepatic impairment. [HA749 trade name] must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2).

Renal impairment

No dosage adjustment is needed. [HA749 trade name] is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2).

Pregnancy and postpartum

<u>During the second and third trimesters of pregnancy</u>

[HA749 trade name] 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) and clinical monitoring may be considered to ensure adequate exposure.

The risk of a further decrease in atazanavir exposure is expected when [HA749 trade name] is given with medicinal products known to reduce its exposure (e.g., tenofovir disoproxil or H2-receptor antagonists). It is not recommended to use [HA749 trade name] for pregnant patients who are receiving both tenofovir disoproxil and an H2-receptor antagonist.

- If tenofovir disoproxil or an H_2-receptor antagonist is needed, a dose increase to atazanavir 400 mg with ritonavir 100 mg, with TDM may be considered (see sections 4.6 and 5.2). Other pharmaceutical forms/strengths of atazanavir/ritonavir should be administered to patients in this circumstance.
- It is not recommended to use [HA749 trade name] for pregnant patients who are receiving both tenofovir disoproxil and an H2-receptor antagonist.

<u>Postpartum</u>

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).

Method of administration

[HA749 trade name] should be swallowed whole and not be cut, dissolved, chewed, broken or crushed.

4.3 Contraindications

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

[HA749 trade name] is contraindicated in patients with moderate and severe hepatic insufficiency (see sections 4.2, 4.4 and 5.2).

Ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated drug metabolism. Furthermore, atazanavir and ritonavir are themselves substrates for CYP3A4. The following medicines are contraindicated when [HA749 trade name] is used due to the risk of adverse effects or loss of efficacy due to drug-drug interactions (see also sections 4.2, 4.4. and 4.5.):

Medicinal Product Class	**Medicinal Products within Class**	**Rationale**
α1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension.
Analgesics	Propoxyphene	Increased plasma concentrations of
Medicinal Product Class	**Medicinal Products within Class**	**Rationale**
		propoxyphene, thereby increasing the risk of serious respiratory depression.
Antiarrhythmics	Amiodarone, flecainide, quinidine	Increased plasma concentrations of antiarrythmics increase the risk of arrhythmias or other serious adverse reactions from these agents (see section 4.5).
Antibacterials	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anticoagulants	Apixaban, rivaroxaban	Increased plasma concentrations with potential higher risk of bleeding.
	Clopidogrel	Decreased clinical activity of clopidogrel.

Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine, thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterials	Rifampicin, rifapentine	Decreased plasma concentration of atazanavir which can result in virological failure and resistance development (see section 4.5).
Antineoplastics	Irinotecan	Interference with irinotecan metabolism leading to increased toxicity (see also section 4.5).
	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life- threatening reactions including hepatotoxicity.
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life- threatening reactions.
	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide, thereby increasing the risk of serious haematologic abnormalities, cardiovascular or other serious adverse effects from these agents.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma.
Antiviral, for hepatitis C	Elbasvir/grazoprevir, glecaprevir/pibrentasvir	Increased plasma concentration of grazoprevir and elbasvir which is associated with increase in risk of ALT elevations.
Ergot derivatives	Dihydroergotamine, ergometrine, ergotamine, methylergometrine	Increased plasma concentrations of ergot derivatives leading to acute

		ergot toxicity, including vasospasm and ischaemia.
Lipid-modifying agents (HMG Co-A reductase inhibitors)	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis.
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (see section 4.5).

Medicinal Product Class	**Medicinal Products within Class**	**Rationale**
PDE5 inhibitors	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil, thereby increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope). See section 4.4 and section 4.5 for coadministration of sildenafil in patients with erectile dysfunction.
Proton pump inhibitors	Lansoprazole, omeprazole, pantoprazole	Decreased plasma concentrations and reduced clinical effects of atazanavir. (for advice if coadministration is unavoidable see section 4.5).
Sedatives/hypnotics	Oral midazolam, triazolam	Greatly increased plasma concentrations of oral midazolam and triazolam may increase the risk of extreme sedation and respiratory depression from these agents. (For caution on other benzodiazepines including parenterally administered midazolam, see section 4.5).

Herbal preparation	St. John's wort	Risk of decreased plasma concentrations and reduced clinical effects of [HA749 trade name].

4.4 Special warning and precautions for use

Opportunistic infections

Patients receiving [HA749 trade name] may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

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 [HA749 trade name] 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.

[HA749 trade name] should not be given to patients with decompensated liver disease (see section 4.2). 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 to the relevant product information for these medicinal products. 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, [HA749 trade name] is not recommended in patients undergoing haemodialysis (see sections 4.2 and 5.2).

PR interval 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), [HA749 trade name] should be used with caution and only if the benefits exceed the risk (see section 5.1).

Particular caution should be used when prescribing [HA749 trade name] 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.

Hyperlipidaemia

Combination antiretroviral therapy, including atazanavir/ritonavir-based regimens, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section4.8).

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

Hyperglycaemia

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

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 [HA749 trade name] 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.

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.

Osteonecrosis

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

Rash and associated syndromes

Rashes are usually mild -to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with [HA749 trade name].

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 [HA749 trade name]. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. [HA749 trade name] should be discontinued if severe rash develops.

Early diagnosis and immediate interruption of any suspect medicines are important in the management of such events. If the patient has developed SJS or DRESS associated with the use of [HA749 trade name], [HA749 trade name] should be permanently discontinued.

Gastric pH

The bioavailablity of atazanavir is pH dependent, and absorption is reduced in

situations where gastric pH is increased, irrespective of cause. Therefore, co-administration of [HA749 trade name] and medicines to control gastric acidity requires caution and may be best avoided (see section 4.5.)

Contraception

Co-administration of [HA749 trade name] 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).

When [HA749 trade name] is co-administered with estradiol-containing contraceptives, barrier or other non- hormonal methods of contraception should be considered as [HA749 trade name] is likely to reduce the contraceptive effect and change the uterine bleeding profile.

Ritonavir dosed as a pharmacokinetic enhancer

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, hyperbilirubinemia) and therefore is not recommended. In situations where dose adjustment of atazanavir or ritonavir are considered clinically necessary, alternative formulations should be used.

Excipients

[HA749 trade name] contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

[HA749 trade name] contains atazanavir and ritonavir, both of which are inhibitors of cytochrome P450 (CYP) isoforms. When [HA749 trade name] is administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

[HA749 trade name] is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, [HA749 trade name] 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, and ergot alkaloids, particularly ergotamine and dihydroergotamine (see section 4.3).

Co-administration of [HA749 trade name] 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 [HA749 trade name] with glecaprevir/pibrentasvir fixed dose combination is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecapreir and pibrentasvir plasma concentrations (see section 4.3)

Co-administration of [HA749 trade name] and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For selected medicinal products (e.g. alprazolam) the inhibitory effects of [HA749 trade name] on CYP3A4 may decrease over time.

Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time (e.g. digoxin and fexofenadine-see table "Ritonavir effects on non-antiretroviral medicinal products" below). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19, thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect.

Serum levels of ritonavir can be reduced by concomitant use of herbal preparations containing St John's wort (*Hypericum perforatum*). This is due to the induction of medicinal product metabolising enzymes by St John's wort. Herbal preparations containing St John's wort must not be used in combination with [HA749 trade name]. If a patient is already taking St John's wort, St John's wort should be stopped and if possible check viral levels. Ritonavir levels may increase on stopping St John's wort. The dose of ritonavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).Atazanavir inhibits UGT and can reduce clearance of active substances that rely on glucuronidation.

Other interactions

Interactions between atazanavir /ritonavir and co-administered medicinal products are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔").

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
ANTI-HCV AGENTS		

Boceprevir	bocepre vir AUC ↔ Cmax ↔ Cmin ↔ atazana vir AUC ↓ Cmax ↓ Cmin ↓ ritonavir AUC ↓ Cmax ↓ ritonavir Cmin ↓ 45%	Co-administration of atazanavir/ritonavir with boceprevir resulted in lower exposure of atazanavir which may be associated with lower efficacy and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring for HIV suppression is warranted.
Grazoprevir	Atazanavir AUC ↑ Cm ax ↑ Cmi n ↑ Grazopr evir AUC: ↑ Cm ax ↑ Cmi n ↑ Grazoprevir concentrations were greatly increased when co- administered with atazanavir/ritonavir.	Co-administration of [HA749 trade name] and elbasvir/grazoprevir is contraindicated because of a significant increase in grazoprevir plasma concentrations andan associated potential increase in the risk of ALT elevations.

Elbasvir	Atazanavir AUC ↑ Cmax ↑ Cmin ↑ Elbasvir AUC ↑ Cmax ↑ Cmin ↑ Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir.	
Sofosbuvirvelpatasvir /voxilaprevir	Sofosbuvir AUC ↑ Cmax ↑	Co-administration of [HA749 trade name] with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Coadministration of [HA749 trade name] with

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
	Velpatasvir AUC↑ Cmax ↑ AUC ↑ Cmax ↑ Effect on atazanavir and ritonavir exposure has not been studied. Expected: ↔ Atazanavir ↔ Ritonavir The mechanism of interaction between [HA749 trade name] and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, Pgp, and CYP3A.	voxilaprevir-containing regimens is not recommended.
Glecaprevir Pibrentasvir	Glecaprevir AUC ↑ Cmax ↑ Cmin ↑ Pibrentasvir AUC ↑ Cmin ↑	Co-administration of [HA749 trade name] with glecaprevir/pibrentasvir is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations.
Simeprevir	Simeprevir AUC ↑ Cmax ↑ Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition.	It is not recommended to coadminister [HA749 trade name] with simeprevir.
ANTIRETROVIRALS		
Protease inhibitors: The coadministration of [HA749 trade name] and other protease inhibitors has not been studied but would be expected to increase		

exposure to other protease inhibitors. Therefore, such coadministration is not recommended.		
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Coadministration of [HA749 trade name] and indinavir is not recommended (see section 4.4).
Amprenavir	Amprenavir **AUC** ↑ Amprenavir **C_{min}** ↑	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. For further information, physicians should refer to the Summary of Product Characteristics for amprenavir.
Darunavir	Darunavir **AUC** ↑	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
		ritonavir to ensure its therapeutic effect. Ritonavir doses higher than 100 mg twice daily have not been studied with darunavir. For further information, refer to the Summary of Product Characteristics for darunavir
Fosamprenavir	Amprenavir AUC ↑ Amprenavir C_{min} ↑	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. Clinical trials confirmed the safety and efficacy of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily. Ritonavir doses higher than 100 mg twice daily have not been studied with fosamprenavir. For further information, physicians should refer to the Summary of Product Characteristics for fosamprenavir.

Nelfinavir	Nelfinavir AUC ↑ Ritonavir Cmin ↔ AUC ↔	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir- mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily
Saquinavir	Saquinavir AUC ↑ Cmin ↑ Ritonavir Cmin ↔ AUC ↔	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir100 mg twice daily with saquinavir 1000 mg twice daily provides saquinavir systemic exposure over 24 hours similar to or greater than those achieved with saquinavir 1200 mg three times daily without ritonavir. In a clinical study investigating the interaction of rifampicin 600 mg once daily and saquinavir 1000 mg with ritonavir 100 mg twice daily in healthy volunteers,

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
		severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of coadministration was noted. Due to the risk of severe hepatoxicity, saquinavir/ritonavir should not be given together with rifampicin. For further information, physicians should refer to the Summary of Product Characteristics for saquinavir.
Tipranavir	Tipranavir AUC ↑ Cmin ↑ Ritonavir AUC ↓ C_{min} Not determined	Ritonavir increases the serum levels of tipranavir as a result of CYP3A inhibition. Tipranavir must be given with low dose ritonavir to ensure its therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used with tipranavir as they might alter the efficacy of the combination. For further information, physicians should refer to the Summary of Product Characteristics for tipranavir.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine + zidovudine	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 coadministration of these medicinal products and [HA749 trade name] is not expected to significantly alter the exposure of the coadministered medicinal products.
Abacavir	The coadministration of abacavir and [HA749 trade name] is not expected to significantly alter the exposure of abacavir.	
Didanosine (buffered tablets)	Atazanavir, simultaneous administration with ddI+d4T (fasted) Atazanavir AUC ↓ Cmax ↓ Cmin ↓	Didanosine should be taken at the fasted state 2 hours after [HA749 trade name] taken with food. The coadministration of stavudine with [HA749 trade name] is not expected to significantly alter the exposure of stavudine.
	Atazanavir, dosed 1 hr after ddI+d4T (fasted) Atazanavir AUC ↔	

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**

	Cma x ↑ Cmi n ↔ Atazanavir concentrations were greatly decreased when coadministered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.	
Didanosine (enteric coated capsules)	Didanosine (with food) AUC ↓ Cm ax ↓ Cmi n ↑ 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 tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil. Studies conducted in HIV- infected patients	Atazanavir AUC ↓* Cmax ↓* Cmin ↓* *In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg coadministered with tenofovir disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33). The efficacy of [HA749 trade name] in combination with tenofovir disoproxil fumarate in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir disoproxil fumarate is unknown. Tenofovir disoproxil fumarate AUC ↑ Cmax ↑ Cmin ↑	When coadministered tenofovir disoproxil fumarate with [HA749 trade name], tenofovir disoproxil fumarate 300 mg (all as a single dose with food) is recommended. Patients should be closely monitored for tenofovir disoproxil fumarate-associated adverse reactions, including renal disorders.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Efavirenz	Atazanavir AUC ↔ Cmax ↑ Cmin ↓	Coadministration of efavirenz and [HA749 trade name] is not recommended. If the coadministration of [HA749 trade name] with an NNRTI is required, using other formulations to allow an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered, with close clinical monitoring.
Nevirapine Study conducted in HIV infected patients	Nevirapine AUC ↑ Cmax ↑ Cmin ↑ Atazanavir AUC ↓* Cmax ↔* Cmin ↓* * When compared to 300 mg and ritonavir 100 mg without nevirapine. This decrease in atazanavir Cmin, might negatively impact the efficacy of atazanavir. The mechanism of nevirapine/atazanavir	Coadministration of nevirapine and [HA749 trade name] is not recommended

	interaction is CYP3A4 induction.	
Integrase inhibitors		
Raltegravir	Raltegravir AUC ↑ Cmax ↑ C12hr ↑ The mechanism is UGT1A1 inhibition.	No dose adjustment required for raltegravir.
ANAESTHETICS AND MUSCLE RELAXANTS		
Ketamine	Coadministration may increase comedication exposure.	A dose adjustment may be needed. Monitor clinical effect.
ANTIBACTERIALS		
Azithromycin	Coadministration may increase comedication exposure.	No prior dose adjustment is recommended. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Bedaquiline	Coadministration may increase comedication exposure.	Caution is recommended as both drugs have risks of QT prolongation. More frequent ECG monitoring and monitoring of transaminases is recommended. Coadministration for more than 14 consecutive days should be avoided.
Clarithromycin	Clarithromycin AUC ↑ Cmax ↑ Cmin ↑ 14-OH clarithromycin AUC ↓ Cmax ↓ Cmin ↓ Atazanavir AUC ↑ Cmax ↔ Cmin ↑ A dose reduction of clarithromycin may result in subtherapeutic concentrations of 14-OH clarithromycin. The mechanism of the clarithromycin/atazanavir interaction is CYP3A4 inhibition.	Clarithromycin doses greater than 1 g per day should not be coadministered with [HA749 trade name]. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 mL/min, the dose should be reduced by 50%; for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.

Erythromycin	Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin.	Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is used concomitantly with [HA749 trade name].
Fusidic acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir.	Coadministration of fusidic acid and [HA749 trade name] is contraindicated .
ANTIFUNGALS		
Ketoconazole	Coadministration may increase ketoconazole exposure.	The daily dose of ketoconazole should not exceed 200 mg. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Itraconazole	Coadministration may increase itraconazole exposure.	The daily dose of itraconazole should not exceed 200 mg. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
Voriconazole Subjects with at least one functional CYP2C19 allele	Voriconazole AUC ↓ Cmax ↓ Cmin ↓ Atazanavir AUC ↓ Cmax ↓ Cmin ↓ Ritonavir AUC ↓ Cmax ↓ Cmin ↓ In the majority of patients with at least one functional CYP2C19 allele, a reduction in both voriconazole and atazanavir exposures are expected.	Coadministration of voriconazole is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. The effect of atazanavir/ritonavir on voriconazole exposure is dependent on CYP2C19 metaboliser status – exposure increased in extensive metaboliser and decrease in poor metabolisers. Patients should be carefully monitored for voriconazole-associated adverse reactions and loss of voriconazole efficacy. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.

oriconazole Subjects without a functional CYP2C19 allele.	Voriconazole AUC ↑ Cmax ↑ Cmin ↑ Atazanavir AUC ↓ Cmax ↓ Cmin ↓ Ritonavir AUC ↓ Cmax ↓ Cmin ↓ In a small number of patients without a functional CYP2C19 allele, significantly increased voriconazole exposures are expected.	
Fluconazole	No pharmacokinetic interaction expected.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended
ANTIMALARIALS		
Chloroquine	Coadministration may increase chloroquine exposure to a moderate extent.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
Artemisinin	Coadministration may increase	A dose adjustment may be

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
	comedication exposure.	needed. Monitor clinical effect.
Hydroxychloroquine	Coadministration may increase comedication exposure to a moderate extent.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended
Lumefantrine	Coadministration may increase comedication exposure.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
Mefloquine	Coadministration may increase comedication exposure.	Caution and close monitoring is recommended as both drugs have risks of QT prolongation.
Primaquine	No pharmacokinetic interaction expected.	Caution and close monitoring is recommended as both drugs have risks of QT prolongation.
Proguanil	Coadministration decreased proguanil exposure.	Coadministration of atovaquone/proguanil should be avoided whenever possible. If judged clinically necessary, consider taking atovaquone/ proguanil with a high fat meal to increase its bioavailability and increase the dosage if required.
Quinine	Coadministration may increase comedication exposure.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
ANTIMYCOBACTERIALS/TB TREATMENTS		

Delamanid	Coadministration may increase comedication exposure.	Increased exposure to delamanid metabolites has been associated with QTc prolongation. If coadministration of delamanid with [HA749 trade name] is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended.
Levofloxacin	No pharmacokinetic interaction expected.	Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
Moxifloxacin	Coadministration may decrease moxifloxacin exposure.	Monitor clinical effect and increase dose if needed. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
Rifabutin	Rifabuti n AUC ↑ ** Cmax ↑** Cmin ↑** 25-O-desacetyl- rifabutin AUC ↑**	When given with [HA749 trade name], the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
	Cmax ↑** Cmin ↑** ** When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl- rifabutin AUC ↑119% (↑78% ↑169%). In previous studies, the pharmacokinetics of atazanavir was not altered by rifabutin.	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 [HA749 trade name].
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 [HA749 trade name] or other protease inhibitors with ritonavir, a high frequency of liver reactions was seen.	The combination of rifampicin and [HA749 trade name] is contraindicated.

Rifapentine	The magnitude of rifapentine- mediated CYP3A4 induction is predicted to be lower than with rifampicin but higher than with rifabutin	The combination of rifapentine and [HA749 trade name] is contraindicated in WHO guidelines. May significantly decrease atazanavir/ritonavir concentrations which may reduce the therapeutic effect. Consider using rifabutin.
ACID REDUCING AGENTS		
H2-Receptor antagonists		
Without Tenofovir		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily		**For patients not taking tenofovir,** if [HA749 trade name] 300 mg/ritonavir 100 mg and H2-receptor antagonists are co-administered, a dose equivalent to famotidine 20 mg twice daily should not be exceeded.
Famotidine	Atazanavir AUC ↓ Cmax ↓ Cmin ↔	
With Tenofovir disoproxil fumarate 300 mg once daily (equivalent to 245 mg tenofovir disoproxil)		
In HIV-infected patients with atazanavir/ritonavir at the recommended dose of 300/100 mg once daily		**For patients who are taking tenofovir disoproxil fumarate,** if [HA749 trade name] with both tenofovir disoproxil fumarate and an H2-receptor
Famotidine	Atazanavir AUC ↓* Cmax ↓* Cmin ↓*	

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
In HIV-infected patients with atazanavir/ritonavir at an increased dose of 400/100 mg once daily		antagonist are coadministered, a dose increase of [HA749 trade name] 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 ↑* Cmax ↑* Cmin ↑*	
Famotidine 40 mg twice daily	Atazanavir AUC ↔* Cmax ↔* Cmin ↔*	
	* When compared to atazanavir 300 mg once daily with ritonavir 100 mg once daily and tenofovir disoproxil fumarate 300 mg all as a single dose with food. When compared to atazanavir 300 mg with ritonavir 100 mg *without tenofovir disoproxil fumarate*, atazanavir concentrations are expected to be additionally decreased by about 20%. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric Ph increases with H2- blockers.	
Proton pump inhibitors		

Omepraz ole, lansopra zole, pantopra zole	Atazana vir AUC ↓ Cm ax ↓ Cmi n ↓	Coadministration of [HA749 trade name] with proton pump inhibitors is contraindicated in WHO guidelines. If coadministration is judged unavoidable, close clinical monitoring is recommended and doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 hours prior to the atazanavir/ritonavir.
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 [HA749 trade name].	[HA749 trade name] 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	Coadministration of alfuzosin with [HA749 trade name] is contraindicated

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
	by ritonavir and/or atazanavir.	
AMPHETAMINES		
Amphetamine	Ritonavir likely to inhibit CYP2D6 and as a result, is expected to increase concentrations of amphetamine and its derivatives.	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with [HA749 trade name]
ANTHELMINTICS		
Albendazole	No pharmacokinetic interaction is expected with a short duration treatment but the clinical effect of albendazole may be reduced when used for a long duration treatment.	
ANTICOAGULANTS		
Apixaban	Potential for increased apixaban concentrations which can result in a higher risk of bleeding. The mechanism of interaction is inhibition of CYP3A4 / and P-gp by[HA749 trade name]. Ritonavir is a strong inhibitor of both CYP3A4 and P-gp. Atazanavir is an inhibitor of CYP3A4.	Coadministration of apixaban with [HA749 trade name] is contraindicated in WHO guidelines.
Clopidogrel	Ritonavir markedly reduces exposure to the active metabolite of clopidogrel, decreasing the clinical activity.	The combination of clopidogrel and [HA749 trade name] is contraindicated in WHO guidelines.

Dabigatran	Potential for increased dabigatran concentrations which can result in a higher risk of bleeding. The mechanism of interaction is P-gp inhibition. Ritonavir is a strong P-gp inhibitor. Potential P-gp inhibition by Atazanavr is unknown and cannot be excluded.	Coadministration of dabigatran with [HA749 trade name] 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 [HA749 trade name]. Ritonavir is a strong P-gp inhibitor. Potential P-gp inhibition by Atazanavir is unknown and cannot be excluded.	Exercise caution when edoxaban is used with [HA749 trade name]. Please refer to edoxaban SmPC section 4.2 and 4.5 for appropriate edoxaban dosage recommendations for coadministration with P-gp inhibitors.
Heparin		The coadministration of Heparin with [HA749 trade name] is not recommended (see section 4.4 and refer to the Heparin SmPC).
Rivaroxaban	Rivaroxaban AUC ↑153% Rivaroxaban Cmax ↑55% Inhibition of CYP3A and P-gp by ritonavir lead to increased plasma	The use of [HA749 trade name] with rivaroxaban is contraindicated in WHO guidelines.

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
	levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk.	
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir.	The coadministration of vorapaxar with [HA749 trade name] is not recommended.
Warfarin	Coadministration with [HA749 trade name] has the potential to increase or decrease warfarin concentrations.	It is recommended that the International Normalised Ratio (INR) be monitored carefully during treatment with [HA749 trade name], especiallywhen commencing therapy.
ANTIDEPRESSANTS		
Trazodone	An increase in the incidence in trazodone-related adverse reactions was noted when coadministered with ritonavir.	If trazodone is coadministered with [HA749 trade name], the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.
Lithium	No pharmacokinetic interaction expected.	Caution and close monitoring is recommended as both drugs have risks of QT prolongation
ANTI-DIABETICS		

Glibenclamide (Glyburide)	Coadministration may increase comedication exposure.	A dose adjustment may be needed. Monitor clinical effect.
Gliclazide	Coadministration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed.
ANTIEPILEPTICS		
Carbamazepine	[HA749 trade name] may increaseplasma levels of carbamazepine due to CYP3A4 inhibition. Due to carbamazepine inducing effect, a reduction in [HA749 trade name] exposure cannot be ruled out.	Carbamazepine should be used with caution in combination with [HA749 trade name]. If necessary, monitor carbamazepine serum concentrations and adjust the dose accordingly. Close monitoring of the patient's virologic response should be excercised.
Clonazepam	Coadministration may increase comedication exposure.	A dose adjustment may be needed. Monitor clinical effect.
Phenytoin, phenobarbital, divalproex	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 [HA749 trade name] exposure cannot be ruled out	Phenobarbital and phenytoin should be used with caution in combination with [HA749 trade name]. When [HA749 trade name] is coadministered with either phenytoin or phenobarbital, a

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
		dose adjustment of phenytoin or phenobarbital may be required. Close monitoring of patient's virologic response should be exercised.
Lamotrigine	Coadministration of lamotrigine and [HA749 trade name] may decrease lamotrigine plasma concentrations due to UGT1A4 induction.	Lamotrigine should be used with caution in combination with [HA749 trade name]. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly
Valproate	Coadministration may decrease comedication exposure.	Monitor clinical effect and increase dose if needed
ANTI-GOUT TREATMENTS		
Colchicine	Coadministration may increase colchicine exposure. Refer to the product label for dose recommendations for the treatment/prophylaxis of gout flares and the treatment of familial Mediterranean fever.	Coadministration is contraindicated in patients with renal or hepatic impairment.
ANTIHISTAMINES		
Astemizole, terfenadine	Ritonavir coadministration is likely to result in increased plasma concentrations of astemizole and terfenadine.	Coadministration of [HA749 trade name] and astemizole or terfenadine is contraindicated.
Loratadine	Ritonavir inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine.	Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly

		administered with [HA749 trade name].
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.	Increased fexofenadine levels may lessen over time as induction develops,
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		
Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir.	Coadministration of abemaciclib and [HA749 trade name] should be avoided. If this coadministration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
Afatinib	Afatinib AUC ↑ C_{max} ↑	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
		of ritonavir administration. Caution should be exercised in administering afatinib with [HA749 trade name] (refer to the afatinib SmPC). Monitor for ADRs related to afatinib
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of ritonavir and potential loss of virologic response. In addition, serum concentrations may be increased when coadministered with ritonavir resulting in the potential for serious adverse events including seizure. .	Concomitant use of [HA749 trade name]with apalutamide is not recommended.
Ceritinib	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with [HA749 trade name]	Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse reactions.	
Encorafenib	Serum concentrations may be increased when coadministered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval	Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be

	prolongation.	used, patients should be carefully monitored for safety.
Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome.	Coadministration of ibrutinib and [HA749 trade name] should be avoided. If the benefit is considered to outweigh the risk and [HA749 trade name] must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	WHO guidelines contraindicate use with irinotecan. If [HA749 trade name] is coadministered with irinotecan, patients should be closely monitored for adverse events related to irinotecan.
Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir.	Concomitant use of neratinib with [HA749 trade name]is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).
Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and	Contraindicated at dose initiation and in the ramp-up phase. For patients who have completed these and are on a steady daily

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
	during the ramp-up phase	dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).
Immunosuppressants		
Cyclosporin Tacrolimus Sirolimus Everolimus	Concentrations of these immunosuppressants may be increased when coadministered with [HA749 trade name] due to CYP3A4 inhibition.	More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been established.
ANTIPARKINSONIAN AGENTS		
Carbidopa	Enhanced levodopa effects including severe dyskinesia have been reported with some protease inhibitors.	Monitor for levodopa/carbidopa efficacy.
Levodopa	Enhanced levodopa effects including severe dyskinesia have been reported with some protease inhibitors.	Monitor for levodopa/carbidopa efficacy.
ANTIPSYCHOTICS/NEUROLEPTICS		
Buspirone	Ritonavir inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone.	Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with [HA749 trade name].

Clozapine, pimozide	Ritonavir is likely to result in increased plasma concentrations of clozapine or pimozide.	Coadministration of clozapine or pimozide with [HA749 trade name] is contraindicated due to the increased risk of serious adverse effects.
Fluphenazine	Coadministration may increase fluphenazine exposure.	Caution is recommended as both drugs have risks of QT prolongation. The European product label for fluphenazine contraindicates the concurrent use of other drugs that also prolong the QT interval.
Haloperidol, risperidone, thioridazine	Atazanavir/ritonavir could potentially increase haloperidol exposure although to a moderate extent, and may also increase exposure to risperidone and thioridazine. These antipsychotics may prolong the QT interval.and additive QT prolongation is possible with atazanavir.	Concomitant use of [HA749 trade name]with haloperidol or thioridazine is contraindicated and caution is advised if used with risperidone.
Lurasidone	[HA749 trade name] is expected to increase plasma levels of lurasidone due to CYP3A4 inhibition.	Coadministration of lurasidone with [HA749 trade name] is contraindicated as this may increase lurasidone-related toxicity.
Quetiapine	Due to CYP3A4 inhibition by [HA749 trade name], concentrations of quetiapine are expected to increase.	Coadministration of quetiapine with [HA749 trade name] is contraindicated as [HA749 trade name] may increase

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
		quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.
CARDIOVASCULAR AGENTS		
Antianginal		
Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase.	The concomitant administration of [HA749 trade name] with ranolazine is contraindicated (see section 4.3).
Antiarrhythmics		
Amiodarone, dronedarone, encainide, flecainide, systemic lidocaine propafenone, quinidine .	Concentrations of these antiarrhythmics may be increased when coadministered with [HA749 trade name]. due to CYP3A inhibition. Many antiarrythmics have a narrow therapeutic window and concomitant use may be contraindicated if concentrations and potential adverse effects cannot be closely monitored..	Great caution is warranted and therapeutic concentration monitoring is recommended when available. The concomitant use of [HA749 trade name] with amiodarone, flecainide and quinidine is contraindicated in WHO guidelines (see section 4.3).

Digoxin	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops.	In patients who are already taking digoxin when [HA749 trade name] is introduced, the digoxin dose should be reduced to one-half of the patients' normal dose and patient need to be followed more closely than usual for several weeks after initiating coadministration of [HA749 trade name] and digoxin. In patients who are already taking [HA749 trade name] when digoxin is introduced, digoxin should be introduced more gradually than usual. Digoxin levels should be monitored more intensively than usual during this period, with dose adjustments made, as necessary, based on clinical, electrocardiographic and digoxin level findings.
Calcium channel blockers		
Bepridil	[HA749 trade name] should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Coadministration with bepridil is contraindicated (see section 4.3)

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Diltiazem	Diltiaze m AUC ↑ Cm ax ↑ Cmi n ↑ Desacetyl-diltiazem AUC ↑ Cm ax ↑ Cmi n ↑ No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Coadministration of diltiazem and [HA749 trade name] 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 [HA749 trade name] due to CYP3A4 inhibition.	Caution should be exercised when verapamil is co administered with [HA749 trade name].
CORTICOSTEROIDS		

Fluticasone Budesonide Triamcinolon e	The fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86% (90% confidence interval 82%-89%). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway, e.g., budesonide and triamcinolone. The effects of high fluticasone systemic exposure on ritonavir plasma levels are yet unknown. The mechanism of interaction is CYP3A4 inhibition.	Coadministration of [HA749 trade name] and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may have to be performed over a longer period.
Dexamethasone	Coadministration may increase dexamethasone concentrations.	A dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended. Chronic or high doses of dexamethasone may also

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
		decrease exposure of the antiretroviral drug with the possible loss of therapeutic effect and development of resistance. Use with caution.
Hydrocortisone oral	Coadministration may increase comedication concentrations.	A dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended.
Prednisolone	Coadministration may increase comedication concentrations. The AUC of the metabolite prednisolone increased by 37% and 28% after 4 and 14 days ritonavir, respectively.	A dose adjustment may be required. Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with [HA749 trade name].
Testosterone	Coadministration may increase comedication concentrations.	A dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended.
ENDOTHELIN ANTAGONISTS		
Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir.	The coadministration of riociguat with [HA749 trade name] is not recommended (
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		

Sildenafil, avanafil, tadalafil, vardenafil	Sildenafil, avanafil, tadalafil and vardenafil are metabolised by CYP3A4. Co-administration with [HA749 trade name] 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	If concomitant use cannot be avoided, patients should be warned about these possible side effects when using PDE5 inhibitors for erectile dysfunction with [HA749 trade name] (see section 4.4). Also see PULMONARY ARTERIAL HYPERTENSION in this table for further information regarding co-administration of [HA749 trade name] with sildenafil.
ERGOT DERIVATIVES		
Dihydroergotamine, ergometrine, ergotamine, methylergometrine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives.	Coadministration of [HA749 trade name] with these medicines is contraindicated.
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)	Concomitant use of St. John's wort with [HA749 trade name] 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.	Coadministration of [HA749 trade name] with products containing St. John's wort is contraindicated.

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Garlic	It may decrease exposure of the antiretroviral drug.	Coadministration is not recommended.
Cannabis	Coadministration could decrease cannabis exposure to a moderate extent.	
Cocaine	Coadministration may increase cocaine exposure.	Ensure the patient is aware of signs/symptoms of toxicity. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
Ecstasy (MDMA)	Coadministration may increase comedication exposure.	Ensure the patient is aware of signs/ symptoms of toxicity.
GHB (Gamma-hydroxybutyrate)	Coadministration may increase comedication exposure.	Ensure the patient is aware of signs/ symptoms of toxicity.
LSD (Lysergic acid diethyamide)	Coadministration may increase comedication exposure.	Ensure the patient is aware of signs/ symptoms of toxicity.
Methamphetamine	Coadministration may increase methamphetamine exposure to a moderate extent.	As dosing of recreational drugs can be variable, caution is advised.
HORMONAL CONTRACEPTIVES		

Ethinyloestradiol 25 µg + Norgestimate	Ethinyloestradiol AUC ↓ Cmax ↓ Cmin ↓ Norgestimate AUC ↑ Cmax ↑ Cmin ↑ While the concentration of ethinyloestradiol was increased with atazanavir given alone, due to both UGT and CYP3A4 inhibition by atazanavir, the net effect of atazanavir/ritonavir is a decrease in ethinyloestradiol levels because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	If an oral contraceptive is administered with [HA749 trade name], it is recommended that the oral contraceptive contain at least 30 µg of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen. Coadministration of [HA749 trade name] 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 +	Ethinyloestradiol AUC ↑48% (↑31%	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Norethindrone (atazanavir 400 mg once daily)	↑68%) Ethinyloestradiol Cmax ↑15% (↓1% ↑32%) Ethinyloestradiol Cmin ↑91% (↑57% ↑133%) Norethindrone AUC ↑110% (↑68% ↑162%) Norethindrone Cmax ↑67% (↑42% ↑196%) Norethindrone Cmin ↑262% (↑157% ↑409%) The increase in progestin exposure may lead to related side-effects (e.g. insulin resistance, dyslipidemia, acne and spotting), thus possibly affecting the compliance.	
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Simvastatin Lovastatin	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and coadministration with [HA749 trade name] may result in increased concentrations.	Coadministration of simvastatin or lovastatin with [HA749 trade name] is contraindicated due to an increased risk of myopathy including rhabdomyolysis.
Atorvastatin Rosuvastatin	The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been	Co-administration of atorvastatin or rosuvastatin with [HA749 trade name] is not recommended. If the use of atorvastatin or rovuvastatin is considered strictly

	reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition	necessary, the lowest possible dose of statin should be administered with carefulsafety monitoring (see section 4.4).
Pravastatin Fluvastatin	Coadministration may increase pravastatin and fluvastatin exposure.	Caution should be exercised. It is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
Microsomal triglyceride transfer protein (MTTP) inhibitors		
Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase.	Co-administration of lomitapide with[HA749 trade name] is contraindicated due to a potential risk of markedly increased transaminase levels and hepatotoxicity .
INHALED BETA AGONISTS		
Salmeterol	Co-administration with [HA749 trade name] may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events.	Co-administration of salmeterol with [HA749 trade name] is not recommended.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
	The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	
OPIOIDS		
Buprenorphine	Buprenorphine AUC ↑ Cmax ↑ Cmin ↑ Norbuprenorphine AUC↑ Cmax ↑ Cmin ↑ The mechanism of interaction is CYP3A4 and UGT1A1 inhibition. Concentrations of atazanavir (when given with ritonavir) were not significantly affected.	Co-administration with [HA749 trade name] warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Fentanyl	[HA749 trade name] inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl.	Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with {DotWP-ProductName.
Propoxyphene	[HA749 trade name] co-administration is likely to result in increased plasma concentrations of propoxyphene.	Co-administration of [HA749 trade name] with propoxyphene is therefore contraindicated (see section 4.3).

Methadone	No significant pharmacokinetic interaction expected if methadone is co-administered with [HA749 trade name].	Consider monitoring for withdrawal symptoms. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
Morphine	Coadministration may increase exposure to the active metabolite and potentiate the effects of the opiate in the CNS.	Monitor for sign of opiate toxicity
Pethidine	Pethidine is metabolized mainly by CYP2B6 and to a lesser extent by CYP3A4. Coadministration could potentially decrease pethidine exposure (due to CYP2B6 induction by ritonavir), although the decrease is predicted to be moderate to weak when ritonavir is dosed as a pharmacokinetic booster.	Monitor for signs of toxicity; some authorities recommend to avoid concomitant use with ritonavir
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
Sildenafil	Co-administration with [HA749 trade name] may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-inhibitor- associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir	A safe and effective dose in combination with [HA749 trade name] 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		
Oral Midazolam Triazolam Clorazepate Diazepa m Estazol am Fluraze pam	Midazolam and triazolam are extensively metabolised by CYP3A4. Co-administration with [HA749 trade name] may cause a large increase in the concentration of these benzodiazepines. No drug interaction study has been performed for the co-administration of [HA749 trade name] 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 [HA749 trade name] with triazolam or orally administered midazolam is contraindicated (see section 4.3), whereas caution should be used with co-administration of [HA749 trade name] and parenteral midazolam. If [HA749 trade name] 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

	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam	depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of [HA749 trade name] with clorazepate, diazepam, estazolam and flurazepam requires monitoring of clinical effect and dose adjustment if necessary.
Alprazolam	Alprazolam AUC ↑ 2.5 fold Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed.	Caution is warranted during the first several days when alprazolam is co-administered with [HA749 trade name], before induction of alprazolam metabolism develops.
Zolpidem	Zolpidem AUC ↑ Cmax ↑	Zolpidem and [HA749 trade name] may be co-administered with careful monitoring for excessive sedative effects.
THYROID HORMONE REPLACEMENT THERAPY		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Levothyroxine	Potential interaction between ritonavir containing products and levothyroxine.	Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending [HA749 trade name] treatment.
XANTHINES		
Theophylline	Theophyllin e AUC ↓ Cmax ↓ Caused by ritonavir-induction of CYP1A2	An increased dose of theophylline may be required when coadministered with [HA749 trade name].

4.6Fertility, pregnancy and breastfeeding

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). Use of [HA749 trade name] may be considered in line with official guidelines during pregnancy if the potential benefit justifies the potential risk.

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

Breastfeeding
Atazanavir and ritonavir have been detected in human milk. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility
No human data on the effect of atazanavir and ritonavir on fertility are available. Animal studies do not indicate harmful effects of atazanavir and ritonavir on fertility (see section 5.3).

4.7Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness is a known undesirable effect of [HA749 trade name] (see section 4.8). Patients should be

instructed that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8Undesirable effects

As [HA749 trade name] contains atazanavir and ritonavir, the type and severity of adverse reactions associated with each of the compounds may be expected.

The most frequently reported adverse drug reactions among patients receiving ritonavir were gastrointestinal (including diarrhoea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paraesthesia and oral paraesthesia) and fatigue/asthenia.

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.

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

System Order Class	**Frequency**	**Adverse reaction**
Immune system disorders		Common hypersensitivity, including urticaria and face oedema
	Rare	anaphylaxis
Metabolism and nutrition disorders:	Common	hypercholesterolaemia, hypertriglyceridaemia, gout, oedema, peripheral oedema and dehydration (usually associated with gastrointestinal symptoms), weight decreased
	Uncommon	diabetes mellitus, weight gain, appetite increased Rarehyperglycaemia
Psychiatric disorders:	uncommon	depression, disorientation, anxietysleep disorder and abnormal dream

Nervous system disorders:	Very common	dysgeusia, oral and peripheral paraesthesia, headache, dizziness and peripheral neuropathy
	Common	insomnia, anxiety, confusion, disturbance in attention, syncope and seizure uncommon amnesia and somnolence
Eye disorders	common:	blurred vision and ocular icterus
Cardiac disorders:	uncommon	torsades de pointes, myocardial infarction
	Rare	QTc prolongationa , oedema, palpitation
Vascular disorders	Common	hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders:	very common	pharyngitis, oropharyngeal pain, cough uncommon dyspnoea
Gastrointestinal disorders	very common	abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia
	common	anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
	uncommon	gastritis, abdominal distension, stomatitis aphthous, flatulence and dry mouth, pancreatitis
Hepatobiliary disorders	common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice) uncommon cholelithiasis , cholestasis
	Rare	hepatosplenomegaly, cholecystitis
Skin and subcutaneous tissue disorders:	very common	Pruritus, rash (including erythematous and maculopapular)

System Order Class	Frequency	Adverse reaction
	common	Acne
	uncommon	erythemia multiforme, toxic skin eruptions, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, angioedema , urticaria, alopecia
	Rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), vesiculobullous rash, eczema, vasodilatation
Musculoskeletal and connective tissue disorders	very common	arthralgia and back pain
	common	myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
	uncommon	muscle atrophy
Renal and urinary disorders	common	increased urination, renal impairment (e.g. oliguria, elevated creatinine)
	uncommon	acute renal failure, nephrolithiasis , haematuria, proteinuria, pollakiuria, interstitial nephritis, chronic kidney disease
	Rare	kidney pain
Reproductive system and breast disorders:	common	menorrhagia
	uncommon	gynaecomastia
General disorders and administration site conditions	very common	fatigue including asthenia, flushing, feeling hot common fever
	uncommon	chest pain, malaise,
	Rare	gait disturbance
Blood and lymphatic system disorders	common	decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	uncommon	increased neutrophils

Investigations	common	increased amylase, decreased free and total thyroxin
	uncommon	increased glucose, increased magnesium, increased alkaline phosphatase

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).

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis (see section 4.4).

Laboratory abnormalities

The most frequently reported laboratory abnormality in patients receiving regimens containing ataznavir 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.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9Overdose

Symptoms

There is limited human experience of acute overdose with atazanavir and/or ritonavir.

In clinical trials, single doses of atazanavir 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).

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

Management

There is no specific antidote for overdose with [HA749 trade name]. Treatment of overdose with [HA749 trade name] should consist of general supportive measures, including monitoring of vital signs and electrocardiogram (ECG), and observations of the patient's clinical status. If indicated, administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since both atazanavir and ritonavir are extensively metabolised by the liver and highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

5. Pharmacological products

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors
ATC codes: J05AE08 (atazanavir), J05AE03 (ritonavir)

Mechanism of action

Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus- specific processing of viral *gag-pol* proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells. Atazanavir exhibits anti-HIV-1 (including all clades tested) and anti- HIV-2 activity in cell culture.

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor, which leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little

inhibitory activity against human aspartyl proteases. Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. However, due to ritonavir's potent of inhibition of CYP3A-mediated metabolism, its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor.

Resistance

Antiretroviral treatment naive adult patients

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

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

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

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

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

Antiretroviral treatment experienced adult patients

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

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

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

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

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

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

	Atazanavir	Ritonavir

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

Clinical results

In antiretroviral naive adult patients

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

In antiretroviral experienced adult patients

A randomised, multicenter trial compared atazanavir/ritonavir (300mg/100mg once daily), atazanavir/saquinavir (400mg/1200mg once daily), and lopinavir/ritonavir (400mg/100mg fixed dose combination, twice daily), each in combination with tenofovir (see sections 4.5 and 4.8) and one NRTI, in patients who had failed two or more prior regimens containing at least one PI, NRTI, and NNRTI. Overall, 13% patients in the atazanavir/ritonavir arm and 14% of patients in the lopinavir/ritonavir arm had four or more of the PI substitutions L10, M46, I54, V82, I84, and L90. Thirty-two percent of patients had a viral strain with fewer than two NRTI substitutions.

The primary endpoint was the time-averaged difference in change from baseline in HIV RNA through48 weeks. At 48 weeks the mean changes from baseline in HIV RNA levels for atazanavir/ritonavir and lopinavir/ritonavir were similar/ non-inferior (-1.93 $\log_{10}$ copies/ml for atazanavir/ritonavir and -1.87 $\log_{10}$ copies/ml for lopinavir/ritonavir), and the time-averaged difference was 0.13 $\log_{10}$ copies/mL (atazanavir/ritonavir -lopinavir/ritonavir). Treatment response was durable through 96 weeks. The combination of atazanavir and saquinavir was inferior to lopinavir and ritonavir.

5.2 Pharmacokinetic properties

Absorption of [HA749 trade name]

The absorption characteristics of [HA749 trade name] have been determined after administration of a single dose tablet in healthy subjects under fed condition as follows:

	AUC	C_{max}
Moderate or high fat meal	20-23%↓↑	20-23%↓↑

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**	
	Atazanavir	**Ritonavir**
Maximum concentration (C_{max})	4813 ± 684 (4744) ng /mL	2262 ± 504 (2198) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	50087 ± 9870 (48747) ng ·h/mL	15075 ± 3904 (14554) ng · h/mL
Time to attain maximum concentration (Tmax)	2.77 ± 0.67 h	4.00 ± 0.47 h

Pharmacokinetics of Atazanavir and Ritonavir

Absorption		
Absolute bioavailability	Not determined	Not determined
Oral bioavailability	68%	Not available
Food effect	Co-administration of atazanavir and ritonavir with food optimises the bioavailability of atazanavir.	

	AUC	Cmax	Ctau
Light meal	33%□	40%□	40%□
High fat	No effect relative to fasting state	Within 11% of fasting values	33%□

Distribution		
Volume of distribution (mean)	Not available	20-40l (after a single 600 mg dose)
Plasma protein binding	86%	98 - 99%

in vitro		
Tissue distribution	Distributes to the cerebrospinal fluid and semen	Distributes to the cerebrospinal fluid and semen
Metabolism		
	Principally metabolised by CYP3A4 isozyme to oxygenated metabolites	Extensively metabolised mainly by CYP3A, and by CYP2D6 .
Active metabolite(s)	None	None
Elimination		
Elimination half life	Approximately 12 hours (following a dose of 300 mg once daily with 100 mg ritonavir)	5 h (100 mg twice daily or once daily)
Mean systemic clearance (Cl/F)	Not available	17 ± 7 l/h (100 mg once daily dose)
% of dose excreted in urine	13% (7% unchanged drug)	11.3% (3.5% unchanged drug)
% of dose excreted in faeces	79% (20% unchanged drug)	86% (34% unchanged drug)
Pharmacokinetic linearity	Non-linear pharmacokinetics	-
Drug interactions *(in vitro*)		
Transporters	Substrate for P-gp, MRP, BCRP. May inhibit P-gp, MRP and OATP.	Substrate for P-gp, MRP1. May inhibit P-gp, MRP, OATP-c an BCRP.
Metabolizing enzymes	Substrate and inhibitor of CYP3A4. May inhibit CYP2C8 and UGT1A1.	Substrate for CYP3A and CYP2D6. May inhibit CYP3A4 and 2D6 and induce CYP1A2,, 2C8, 2C9, 2C19 and glucuronidation.

Special populations

Impaired renal function

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.)

Impaired hepatic function

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

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

Children

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 (Cmin, Cmax and AUC) in paediatric patients are expected to be similar to those observed in adults

5.3 Preclinical safety data

Atanazavir

In repeat-dose toxicity studies conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis.

During *in-vitro* studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 μM) of atazanavir corresponding to 30-fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in the rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

In a fertility and early embryonic development study in rats, atazanavir altered oestrus cycling with no effects on mating or fertility. No teratogenic effects were observed in rats or rabbits at maternally toxic doses. In the pre- and postnatal development assessment in rats, atazanavir produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to atazanavir at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg once daily.

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic

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

Ritonavir

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs.
Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration,chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

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

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

6.Pharmaceutical particulars

6.1 List of xcipients

Core tablet: Lactose monohydrate

Partially pregelatinized

starch Crospovidone

Calcium silicate

Ferric oxide
yellow
Magnesium
stearate
Copovidone
Colloidal silicon dioxide
Sorbitan monolaurate
Dicalcium phosphate
anhydrous Sodium
stearyl fumarate

Film coat: Polyvinyl alcohol partially
hydrolysed Talc
Macrogol
Titanium
dioxide Iron
oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Avoid excursions above 30°C. Store in the original container.

6.5 Nature and contents of container

White opaque HDPE bottle with an oxygen-absorbing pouch and a polypropylene closure. Each closure consists of a polypropylene liner and a saf-cap. Pack size: 30 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7.Marketing Authorization Holder

SHANGHAI DESANO BIO-PHARMACEUTICAL CO., LIMITED

8.Marketing Authorisation number

CTD 10795

9.Date of first registration

25/10/2023

10.Date of revision of the text

5/20/2025