Atazor-R
Atazanavir 300 mg/Ritonavir 100 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Atazor-R tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Atazanavir sulphate equivalent to Atazanavir …….....300 mg

Ritonavir USP……100 mg

Excipients: Lactose Monohydrate, Crospovidone, Purified Water, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Sorbiton Monolaurate, Polyoxyl 35 Castor OIL, Opadry Yellow 15B82855

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of HIV-1 infection in adults, in combination with other antiretroviral agents.

4.2 Posology and method of administration

Atazor-R should be administered by physicians who are experienced in the treatment of HIV infection

Posology

This drug is administered only to adults, and the dose should be individualized to each patient based on the effectiveness and tolerability of atazanavir/ritonavir.

The recommended dose is one tablet taken once daily with food.

The fixed- dose combination is not suitable for initial therapy.

If you are taking both atazanavir and ritonavir, you can switch to this combination product having the same content of each active ingredient for convenience.

If a dosage adjustment is necessary, titration should be done with the individual components.

The recommended oral dosage of atazanavir/ritonavir depends on the treatment history of the patient and the use of other coadministered drugs.

Special population
Paediatric population:
The usage in children is limited

Patients with renal impairment:
Atazor-R is not recommended in patients undergoing hemodialysis. It may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency depending on the specific protease inhibitor with which it is coadministered.

Patients with hepatic impairment:
The coadministration of atazanavir with ritonavir in patients with any degree of hepatic impairment is not recommended.

Elderly:
In general, appropriate caution should be exercised in the administration and monitoring of Atazor-R in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pregnancy and Postpartum
<u>During the second and third trimesters of pregnancy</u>:
Atazanavir/ritonavir tablets may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.
The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to reduce its exposure (e.g., tenofovir disoproxil fumarate or H2-receptor antagonists).
• If tenofovir disoproxil or an H2-receptor antagonist is needed, a dose increase to atazanavir 400 mg with ritonavir 100 mg with TDM may be considered.
• It is not recommended to use Atazor-R for pregnant patients who are receiving both tenofovir disoproxil and an H2-receptor antagonist.

<u>During 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. 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.

Method of administration:

Atazor-R is to be administered orally and should be ingested with food.

4.3 Contraindications

- Atazor-R is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed.
- Patients with moderate to severe hepatic insufficiency.
- Co-administration with grazoprevir-containing products, including elbasvir/grazoprevir fixed dose combination (used to treat chronic hepatitis C infection) (see section 4.5).
- Coadministration with glecaprevir/pibrentasvir fixed dose combination.
- C0administration with products containing St. John's wort (*hypericum perforatum*)
- Coadministration of atazanavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in the following Table 1.

Table 1. Drugs that are contraindicated with atazanavir/ritonavir

Drug class	**Drugs within class that are contraindicated with Atazanavir/ ritonavir**	**Clinical Comments**
Alpha 1-adrenoreceptorantagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension

Antimycobacterial	Rifabutin	Concomitant use of ritonavir dosed as an antiretroviral agent (500 mg twice daily) and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse reactions, including uveitis. Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted.
Antibiotics	Rifampicin	Combination of rifampicin and atazanavir is contraindicated
Ergot derivatives	Dihydroergotamine, ergonovine,	Increased plasma concentrations of ergot derivatives leading to acute

	ergotamine, methylergonovin	toxicity, including vasospasm and ischaemia.
GI motility agent	Cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk for serious arrhythmias.
Herbal Products	St John's wort (Hypericum perforatum)	May reduce plasma concentrations of atazanavir and reduced clinical effects of ritonavir. This may result in loss of therapeutic effect and development of resistance.
Lipid-modifying agents HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
PDE5 Inhibitor	Avanafil	Increased plasma concentrations of avanafil
	Vardenafil	Increased plasma concentrations of vardenafil.
	Sildenafil when dosed for the treatment of pulmonary arterial	There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Analgesics	Pethidine, piroxicam, Propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic

		other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions.
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose-titration phase
Antiarrthymics	Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone,	Increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, and quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine.

		increasing the risk of serious arrhythmias from these agents
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated
	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterally administered midazolam.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken.

Patients with coexisting conditions:

Hepatic impairment

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, this product is not recommended in patients undergoing haemodialysis

Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice.

QT prolongation

Dose related asymptomatic prolongation in PR interval with atazanavir have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongation. In patients with pre-existing conduction problems

(second degree or higher atrioventricular or complex bundle-branch block), atazanavir should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing atazanavir 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).

PR interval prolongation

Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products known to prolong the PR interval have been reported in patients receiving ritonavir. Atazor R should be used with caution in such patients.

Patients with chronic diarrhoea or malabsorption:

Extra monitoring is recommended when diarrhoea occurs. The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medicinal products. Serious persistent vomiting and/or diarrhoea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment.

Haemophiliac patients

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to the disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight

gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.
In clinical studies, atazanavir/ritonavir has been shown to induce dyslipidemia to a lesser extent than comparators.

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

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

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

Hyperbilirubinemia

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

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

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, Pneumocystis jiroveci pneumonia and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary

Autoimmune disorders (such as Graves' disease and Autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

Cholelithiasis

Cholelithiasis has been reported in patients receiving atazanavir. 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. 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.

Osteonecrosis

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

Pancreatitis

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

4.5 Interaction with other medicinal products and other forms of Interaction

When atazanavir and ritonavir are co-administered, the metabolic drug interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir. Atazanavir is metabolised in the liver through CYP3A4. It inhibits CYP3A4. Therefore, atazanavir with ritonavir is contraindicated with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index: alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, orally administered midazolam, and ergot alkaloids, particularly ergotamine and dihydroergotamine.

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

Riociguat/Vorapaxar

The concomitant use of ritonavir is not recommended due to potential increase in riociguat and vorapaxar exposure.

Bedaquiline

Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended.

Delamanid

Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended.

Potential for other drugs to affect atazanavir/ritonavir

Atazanavir is a CYP3A4 substrate; therefore, drugs that induce CYP3A4 may decrease atazanavir plasma concentrations and reduce atazanavir's therapeutic effect and are not recommended.

Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if proton-pump inhibitors, antacids, buffered medications, or H2-receptor antagonists are administered with atazanavir.

See Table 1 for a listing of drugs that are contraindicated for use with atazanavir/ritonavir due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. Please refer to Table 2 for established and other potentially significant drug interactions.

Table 2. Established and other potentially significant drug interactions: alteration in dose or regimen may be recommended based on drug interaction studies or predicted interactions

Concomitant Drug Class: Drug Name	**Effect on concentration of atazanavir or concomitant drug**	**Clinical Comment**
Nucleoside Reverse Transcriptase Inhibitors (NRTIs): didanosine buffered formulations enteric-coated (EC) capsules Didanosine (enteric coated capsules) 400mg single dose	↓ Atazanavir ↓ Didanosine	Didanosine should be taken at the fasted state 2 hours after atazanavir/ritonavir taken with food. The coadministration of atazanavir/ritonavir with stavudine is not expected to significantly alter the exposure of stavudine. No significant effect on atazanavir concentrations was observed when administered with enteric- coated didanosine, but administration with food decreased didanosine concentrations

Delavirdine		Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, dose reduction of ritonavir may be considered.
Zidovudine		Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
Amprenavir	↑ amprenavir	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Atazor-R may increase the serum levels of amprenavir
Darunavir	↑ darunavir	Ritonavir increases the serum levels of darunavir as a result of CYP3A4 inhibition and hence Atazor may increase the serum levels of darunavir
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100	Atazanavir AUC ↓22% (↓35% ↓6%) * Atazanavir C_{max} ↓16% (↓30% ↔0%) * Atazanavir C_{min} ↓23% (↓43%	When co-administered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg and tenofovir

mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil. Studies conducted in HIV- infected patients	↑2%) * * In a combined analysis from several clinical studies, atazanavir/ritonavir 300/100 mg co-administered with tenofovir disoproxil fumarate 300 mg (n=39) was compared to atazanavir/ritonavir 300/100 mg (n=33). The efficacy of atazanavir/ritonavir in combination with tenofovir disoproxil fumarate in treatment-experienced patients has been demonstrated in clinical study 045 and in treatment naive patients in clinical study 138 (see sections 4.8 and 5.1). The mechanism of interaction between atazanavir and tenofovir disoproxil fumarate is unknown	disoproxil fumarate 300 mg (all as a single dose with food).

Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil.	Tenofovir disoproxil fumarate AUC ↑37% (↑30% ↑45%) Tenofovir disoproxil fumarate C_{max} ↑34% (↑20% ↑51%) Tenofovir disoproxil fumarate C_{min} ↑29% (↑21% ↑36%)	Patients should be closely monitored for tenofovir disoproxil fumarate- associated adverse reactions, including renal disorders.

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 atazanavir/ritonavir with these medicinal products is not expected to significantly alter the exposure of the coadministered drugs.
Abacavir		The co-administration of atazanavir/ ritonavir with abacavir is not expected to significantly alter the exposure of abacavir
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 100 mg once daily) + Efavirenz 600 mg once daily (atazanavir 400 mg once daily with ritonavir 200 mg once daily)	↔Atazanavir	Co-administration of efavirenz with atazanavir/ritonavir is not recommended. A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.
Maraviroc		Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase

		exposure
Non-nucleoside Reverse Transcriptase Inhibitors: Nevirapine	↓ Atazanavir ↑Nevirapine	Co-administration of nevirapine with atazanavir/ritonavir is not recommended.
Integrase Inhibitors: Raltegravir	↑ Raltegravir	No dose adjustment required for
HCV Protease Inhibitors: Boceprevir	↔ Boceprevir ↓ Atazanavir ↓ Ritonavir	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.
Protease inhibitors: Ritonavir 100 mg once daily (atazanavir 300 mg once daily) Studies conducted in HIV- infected patients.	Atazanavir AUC: ↑250% (↑144% ↑403%)* Atazanavir C_{max}: ↑120% (↑56% ↑211%)* Atazanavir C_{min}: ↑713% (↑359% ↑1339%)* * In a combined analysis, atazanavir 300 mg and ritonavir 100 mg (n=33) was compared to atazanavir 400 mg without ritonavir (n=28). The mechanism of interaction between atazanavir and ritonavir is	Ritonavir 100 mg once daily is used as a booster of atazanavir pharmacokinetics.
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Co-administration of atazanavir/ritonavir and indinavir is not recommended

Nelfinavir	↑ nelfinavir	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily.
ANTI-HCV AGENTS		
Grazoprevir 200 mg once daily (atazanavir 300 mg / ritonavir 100 mg once daily)	Atazanavir AUC ↑43% (↑30% ↑57%) Atazanavir C_{max} ↑12% (↑1% ↑24%) Atazanavir C_{min} ↑23% (↑13% ↑134%) Grazoprevir AUC: ↑958% (↑678% ↑1339%) Grazoprevir C_{max}: ↑524% (↑342% ↑781%) Grazoprevir C_{min}: ↑1064% (↑696% ↑1602%) Grazoprevir concentrations were greatly increased when co-administered with atazanavir/ritonavir.	Co-administration of atazanavir and elbasvir/grazoprevir is contraindicated because of a significant increase in grazoprevir plasma concentrations and an associated potential increase in the risk of ALT elevations (see section 4.3).

Elbasvir 50 mg once daily (atazanavir 300 mg / ritonavir 100 mg once daily)	Atazanavir AUC ↑7% (↓2% ↑17%) Atazanavir C_{max} ↑2% (↓4% ↑8%) Atazanavir C_{min} ↑15% (↑2% ↑29%)	

	Elbasvir AUC: ↑376% (↑307% ↑456%) Elbasvir C_{max}: ↑315% (↑246% ↑397%) Elbasvir C_{min}: ↑545% (↑451% ↑654%) Elbasvir concentrations were increased when co-administered with atazanavir/ritonavir.	

Sofosbuvir 400 mg / velpatasvir 100 mg /voxilaprevir 100 mg single dose* (atazanavir 300 mg / ritonavir 100 mg once daily)	Sofosbuvir AUC : ↑40% (↑25% ↑57%) Sofosbuvir C_{max} :↑29% (↑9% ↑52%) Velpatasvir AUC: ↑93% (↑58% ↑136%) Velpatasvir C_{max} : ↑29% (↑7% ↑56%) Voxilaprevir AUC : ↑331% (↑276% ↑393%) Voxilaprevir C_{max} : ↑342% (↑265% ↑435%) *Lack of pharmacokinetics interaction bounds 70-143% Effect on atazanavir and ritonavir exposure has not been studied. Expected:	Co-administration of atazanavir with voxilaprevir-containing products is expected to increase the concentration of voxilaprevir. Co-administration of atazanavir with voxilaprevir-containing regimens is not recommended.

	↔ Ritonavir The mechanism of interaction between atazanavir/ritonavir and sofosbuvir/velpatasvir/voxilaprevir is inhibition of OATP1B, Pgp, and CYP3A.	
Glecaprevir 300 mg / pibrentasvir 120 mg once daily (atazanavir 300 mg / ritonavir 100 mg once daily*)	Glecaprevir AUC : ↑553% (↑424% ↑714%) Glecaprevir C_{max} : ↑306% (↑215% ↑423%) Glecaprevir C_{min} : ↑1330% (↑885% ↑1970%) Pibrentasvir AUC : ↑64% (↑48% ↑82%) Pibrentasvir C_{max} : ↑29% (↑15% ↑45%) Pibrentasvir C_{min}: ↑129% (↑95% ↑168%) * Effect of atazanavir and ritonavir on the first dose of glecaprevir and pibrentasvir is reported.	Co-administration of atazanavir with glecaprevir/pibrentasvir is contraindicated because of the potential increase in the risk of ALT elevations due to a significant increase in glecaprevir and pibrentasvir plasma concentrations (see section 4.3)
simeprevir		Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic),	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is

dronedarone, encainide, flecainide, propafenone and quinidine		recommended when available. The concomitant use of these drugs is contraindicated
Antihistamines: astemizole, terfenadine		Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore contraindicated
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.
Loratadine		Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent 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 ritonavir.
Anti-infectives: fusidic acid		Ritonavir co-administration is likely to result in increased plasma

		concentrations of both fusidic acid and ritonavir and is therefore contraindicated
Atovaquone		Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.
Bedaquiline		No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir

		must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended
Delamanid		No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended
Sulfamethoxazole/trimethoprim		Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Antacids and buffered medications	↓ Atazanavir	Atazanavir/ritonavir should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.
Antiasthmatic: theophylline		An increased dose of theophyline may be required when co-

		administered with ritonavir, due to induction of CYP1A2.
Alpha-1 adrenoreceptor antagonist: Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir.	Co-administration of alfuzosin with atazanavir is contraindicated
Amphetamine		Ritonavir dosed as an antiretroviral agent is 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 antiretroviral doses of ritonavir
Anticancer agents: afatinib		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 Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with ritonavir. Monitor for ADRs related to afatinib.

Abemaciclib		Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and ritonavir should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
Ceritinib		Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with ritonavir. 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 co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.
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. Co-administration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
Neratinib		Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with ritonavir is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity
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 during the ramp-up phase For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A

		inhibitors
Anticoagulant: warfarin	Co-administration with atazanavir/ritonavir has the potential to increase or decrease warfarin concentrations.	It is recommended that the INR (International Normalised Ratio) be monitored carefully during treatment with atazanavir/ritonavir, especially when commencing therapy.
Rivaroxaban		Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.
Vorapaxar		Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with ritonavir is not recommended
Antiepileptics: Carbamazepine	↑ Carbamazepine	Carbamazepine should be used with caution in combination with atazanavir/ritonavir. If necessary, monitor carbamazepine serum concentrations and adjust the dose accordingly. Close monitoring of the patient's virologic response should be

		excercised.
Phenytoin, Phenobarbital, divalproex	↓ Phenytoin, ↓ phenobarbital	Phenobarbital and phenytoin should be used with caution in combination with atazanavir/ritonavir. When atazanavir/ritonavir is coadministered with either phenytoin or phenobarbital, a dose adjustment of phenytoin or phenobarbital may be required. Close monitoring of patient's virologic response should be exercised.
Lamotrigine	↓ Lamotrigine	Lamotrigine should be used with caution in combination with atazanavir/ritonavir. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly.

Antidepressant: trazodone	↑ Trazodone	Increase in the incidence in trazodone-related adverse reactions was noted when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If trazodone is co-administered with ritonavir, the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.
Desipramine		The AUC and Cmax of the 2-hydroxy metabolite were decreased 15 and 67%, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir dosed as an antiretroviral agent.

Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline		Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir
Antianginal: ranolazine		Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated
Antibiotics: clarithromycin	↑ Clarithromycin ↓ 14-OH clarithromycin	No recommendation regarding dose reduction can be made; therefore, caution should be exercised if atazanavir/ritonavir is coadministered with clarithromycin.
Antifungals: ketoconazole, itraconazole,	↑ Ketoconazole ↑ Itraconazole	Ketoconazole and itraconazole should be used cautiously with atazanavir/ritonavir. High doses of ketoconazole and itraconazole (>200 mg/day) are not

		recommended.
Voriconazole	↓ Voriconazole ↓ Atazanavir ↓ Ritonavir	Co-administration of voriconazole and atazanavir/ritonavir is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole
Fluconazole	↔Atazanavir ↔ fluconazole	No dosage adjustments are needed for atazanavir/ritonavir and fluconazole.
Antimycobacterial: rifabutin	↑ Rifabutin	Increased monitoring for rifabutin associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin, leading to a risk of rifamycin resistance and a treatment failure. No dose adjustment is needed for atazanavir/ritonavir.
Rifampicin	↓ Atazanavir	The combination of rifampicin and atazanavir with concomitant low-dose ritonavir is contraindicated
Antipsycotics: Quetiapine	↑ Quetiapine	Co-administration of atazanavir/ritonavir with quetiapine is contraindicated as may increase quetiapinerelated toxicity. Increased plasma concentrations of quetiapine may lead to coma
Lurasidone	Atazanavir is expected to	Co-administration of

	increase plasma levels of lurasidone due to CYP3A4 inhibition.	lurasidone with atazanavir is contraindicated as this may increase lurasidone-related toxicity
Clozapine, pimozide		Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated
Haloperidol, risperidone, thioridazine		Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
Benzodiazepines: parenterally administered midazolam, Triazolam	↑ Midazolam ↑ Triazolam	Atazanavir/ritonavir should not be coadministered with triazolam or orally administered midazolam. Whereas caution should be used with co-administration of atazanavir/ritonavir and parenteral midazolam. If atazanavir is coadministered with parenteral midazolam, it should be done in an

		intensive care unit (ICU) or similar setting.
Sedatives/hypnotics: Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam		Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore contraindicated (see section 4.3).
Alprazolam		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 ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
Buspirone		Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent 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 ritonavir.
Sleeping agent: Zolpidem		Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.
Smoke cessation: Bupropion		Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.
Calcium channel blockers: diltiazem, amlodipine, nifedipine	↑ Diltiazem and desacetyl-diltiazem	Caution is warranted. A dose reduction of diltiazem by 50% should

		be considered. ECG monitoring is recommended. Coadministration of atazanavir/ritonavir with diltiazem has not been studied.
Bepridil	Atazanavir/ritonavir should not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil is contraindicated
Verapamil	↑ Verapamil	Caution should be exercised when verapamil is co-administered with atazanavir/ritonavir.
Inhaled beta agonist: salmeterol	↑ Salmeterol	Co-administration with atazanavir/ritonavir may result in increased concentrations of salmeterol and an increase in salmeterol associated adverse events and hence is not recommended
Endothelin antagonists: Bosentan		Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentr ations (Cmax) and area under the curve (AUC).
Riociguat		Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with ritonavir is not recommended

Contraceptive: ethinyl estradiol, norgestimate, norethindrone	↓ Ethinyl estradiol ↑ Norgestimate	Barrier or other non-hormonal methods of contraception should be considered when administering ritonavir at therapeutic or low doses as ritonavir is likely to reduce the effect and change the uterine bleeding profile when coadministered with oestradiol-containing contraceptives. Co-administration of atazanavir/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided.
PDE5 Inhibitors: sildenafil, tadalafil, vardenafil	↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving atazanavir/ritonavir. Co-administration of atazanavir /ritonavir with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse reactions including hypotension, syncope, visual changes and

		prolonged erection. Use of PDE5 inhibitors for erectile dysfunction: • Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. • Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. • Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
Avanafil		Concomitant use of avanafil with ritonavir is contraindicated
HMG-CoA Reductase	↑ Simvastatin	Co-administration of simvastatin or lovastatin

Inhibitors: Simvastatin Lovastatin	↑ Lovastatin	with atazanavir is contraindicated due to an increased risk of myopathy including Rhabdomyolysis.
Atorvastatin	↑ Atorvastatin	Co-administration of atorvastatin with atazanavir is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring.
Pravastatin Fluvastatin	↑ Pravastatin ↑ Fluvastatin	Caution should be exercised.
Antineoplastic: Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. Patients should be closely monitored for adverse events related to irinotecan.	
Immunosuppressants: cyclosporine, Tacrolimus Sirolimus	↑ Immunosuppressants	More frequent therapeutic concentration monitoring of these medicinal products is recommended until plasma levels have been stabilized.
Inhaled Steroid: fluticasone	↑ Fluticasone	Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-

		administration of fluticasone propionate and atazanavir /ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect.
Inhaled, injectable or intranasal propionate, budesonide, triamcinolone		Concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. 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 be required over a longer period
Dexamethasone		Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma

		concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
Prednisolone		Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.
Lipid-modifying agent: 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. Concomitant use of ritonavir with lomitapide is contraindicated
Thyroid hormone replacement therapy: Levothyroxine		Post-marketing cases have been reported indicating a 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 ritonavir treatment.
Opioids: buprenorphine	↑ Buprenorphine ↑ Norbuprenorphine	Coadministration of atazanavir/ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Analgesics: pethidine, piroxicam, propoxyphene		Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine, piroxicam, and propoxyphene and is therefore contraindicated
Fentanyl		Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent 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 ritonavir.
Methadone, stable	No significant effect on methadone concentrations	No dosage adjustment is necessary if methadone is

maintenance dose	was observed.	co-administered with atazanavir and ritonavir.
Morphine		Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.

Proton-pump inhibitors: Omeprazole	↓ Atazanavir	Coadministration of atazanavir with or without ritonavir and omeprazole may result in loss of virologic response and development of resistance. ***In HIV-treatment-naive adult patients***: The proton-pump inhibitor (PPI) dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to Atazor-R. ***In HIV-treatment-experienced adult patients:*** Coadministration of Atazor-R with PPIs is not recommended.
H_2-Receptor antagonists		

Without Tenofovir Famotidine 20 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily) Famotidine 40 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily) Famotidine 40 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 400/100 mg once daily)	↓ Atazanavir ↔ Atazanavir	Coadministration may result in loss of virologic response and development of resistance. ***In HIV-treatment-naive adult patients:*** Atazor-R once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H2-receptor antagonist (H2RA). An H2RA dose comparable to famotidine 20 mg once daily up to a dose comparable to famotidine 40 mg twice daily can be used with Atazor-R in treatment-naive patients. **In treatment-experienced adult patients:** Whenever an H2RA is given to a patient receiving atazanavir with ritonavir, the H2RA dose should not exceed a dose comparable to famotidine 20 mg twice daily, and the atazanavir with ritonavir doses should be administered simultaneously with, and/or at least 10 hours after, the dose of the H2RA. Atazor-R once daily (all as a single dose with food) if taken with an H2RA.

With Tenofovir 300 mg once daily: Famotidine 20 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily) Famotidine 40 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 300/100 mg once daily) Famotidine 20 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 400/100 mg once daily) Famotidine 40 mg twice daily (In HIV-infected patients with atazanavir/ritonavir at the recommended dose 400/100 mg once daily)	↓ Atazanavir ↑ Atazanavir ↔Atazanavir	For patients who are Taking tenofovir, if atazanavir/ritonavir with both tenofovir and an H2-receptor antagonist are coadministered, a dose increase of atazanavir to 400 mg with 100 mg of ritonavir is recommended. A dose equivalent to famotidine 40 mg twice daily should not be exceeded.

Digoxin	↑ Digoxin	Particular caution should be used when prescribing ritonavir in patients taking digoxin since co-administration of ritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels may lessen over time. In patients who are already taking ritonavir 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.
Tipranavir	Co-administered with 200 mg of ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C coinfection, as these patients have an increased risk of hepatotoxicity. Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.	

Fosamprenavir	Co-administration of fosamprenavir with ritonavir in doses greater than 100 mg twice daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended. 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.	
Saquinavir	Doses of ritonavir higher than 100 mg twice daily should not be used. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse reactions. Co-administration of saquinavir and ritonavir has led to severe adverse reactions, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease. Saquinavir/ritonavir should not be given together with rifampicin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three medicines are given together	
Glucocorticoids	Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.	
HERBAL PRODUCTS		
St. John's wort (Hypericum perforatum)		Atazor R must not be used in combination with products containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir.

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Animal data have shown reproductive toxicity. The use of Atazor-R may be considered in pregnancy only when the benefits outweigh the risk to the foetus. In a study, 30% of women who received Atazanavir/ritonavir (300/100 mg) and 62% women on Atazanavir/ritonavir 400/100mg, experienced grades 3 to 4 hyperbilirubinaemia. There were no cases of lactic acidosis observed in the clinical study. It is not known whether Atazor-R administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring should be considered.

Breast-feeding:

Atazanavir has been detected in human milk. It is recommended that HIV infected women would not breast-feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

As dizziness is known undesirable effect, this should be taken into account when driving or using machinery.

4.8 Undesirable Effects

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

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

Assessment of adverse reactions for Atazanavir and ritonavir is based on safety data from

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

Blood and lymphatic system disorders	Common	Decreased WBC, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity, including urticaria and face oedema
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Weight decreased, weight gain, anorexia, appetite increased, diabetes mellitus
	Rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, disorientation, anxiety, insomnia, sleep disorder, abnormal dream
Nervous system disorders:	Very common	Dysgeusia, oral and peripheral paresthesia, dizziness, peripheral neuropathy, headache
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
	Uncommon	Amnesia, somnolence
Eye disorders:	Common	Ocular icterus, blurred vision
Cardiac disorders:	Uncommon	Myocardial infarction, torsades de pointes
	Rare	QTc prolongation, 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, diarrhea (including severe electrolyte imbalance), vomiting, dyspepsia
	Common:	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
	Uncommon	Pancreatitis, Gastritis, abdominal distension,

		stomatitis aphthous, flatulence, dry mouth
Hepatobiliary disorders:	Common	Jaundice, Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
	Uncommon	Cholelithiasis, cholestasis
	Rare	Hepatosplenomegaly, cholecystitis
Skin and subcutaneous tissue disorders:	Very common	Pruritis, rash (including erythematous and maculopapular)
	Common	Acne
	Uncommon	Erythemia multiforme, toxic skin eruptions, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, angioedema, urticaria, alopecia, pruritus
	Rare	Stevens-Johnson syndrome, vesiculobullous rash, eczema, vasodilatation, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders:	Very common:	arthralgia, back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
	Uncommon	Muscle atrophy, arthralgia
	Rare	myopathy
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g, oliguria, elevated creatinine)
	Uncommon	Nephrolithiasis, hematuria, proteinuria, pollakiuria, interstitial nephritis; Acute renal failure, 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, weight loss
	Uncommon	Chest pain, malaise, pyrexia,
	Rare	Gait disturbance
Investigations	Common	Increased amylase, decreased free and total

		thyroxin
	Uncommon	Increased glucose, increased magnesium, increased alkaline phosphatase

Description of selected adverse reactions:

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

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.

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

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). Frequency of this is unknown.

Rash and associated syndromes

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

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

Laboratory abnormalities:

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). elevated creatine kinase (7%), elevated alanine aminotransferase/serum glutamicpyruvic transaminase (ALT/SGPT) (5%), low neutrophils (5%), elevated aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (3%), and elevated lipase (3%).

4.9 Overdose

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

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

The signs of toxicity observed in animals (mice and rats) included decreased activity, ataxia, dyspnoea and tremors.

Treatment:

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

There is no specific antidote for overdose with ritonavir. Treatment of overdose with atazanavir/ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Due to the solubility characteristics and possibility of transintestinal elimination, it is proposed that

management of overdose could entail gastric lavage and administration of activated charcoal. Since atazanavir/ritonavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atazanavir and ritonavir are HIV-1 protease inhibitors (PI).

Mechanism of action:

Atazanavir:

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

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

Ritonavir as a pharmacokinetic enhancer:

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor (PI) and the impact of the co-administered PI on the metabolism of ritonavir. Maximal inhibition of metabolism is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily.

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.

5.2 Pharmacokinetic properties

Absorption

Atazanavir 300 mg (when coadministered with ritonavir 100 mg) is rapidly absorbed with a Tmax of approximately 3.0 hours. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and Cmax values over the dose range of 200 to 800 mg once daily. Steady state is achieved between Days 4 and 8, with an accumulation of approximately 2.3 fold.

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability has not been determined. The time to maximum concentration (Tmax) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0.1 l/h and was relatively constant throughout the dosage range.

Food Effect

Administration of Atazanavir with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400-mg dose of Atazanavir with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC and 57% increase in Cmax relative to the fasting state.

Food slightly decreases the bioavailability of the ritonavir film-coated tablets. Administration of a single 100 mg dose of ritonavir film-coated tablets with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and Cmax.

Distribution

Atazanavir is 86% bound to human serum proteins and protein binding is independent of concentration. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively). In a multiple-dose study in HIV-infected patients dosed with Atazanavir 400 mg once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

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

Metabolism

Atazanavir is extensively metabolized in humans. The major biotransformation pathways of atazanavir in humans consisted of monooxygenation and dioxygenation. Other minor biotransformation pathways for atazanavir or its metabolites consisted of glucuronidation, N-dealkylation, hydrolysis, and oxygenation with dehydrogenation. Two minor metabolites of atazanavir in plasma have been characterized.

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent compound. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (PIs) and other products metabolised by CYP3A4) and other PIs may influence the pharmacokinetics of ritonavir.

Elimination

Following a single 400-mg dose of ^{14}C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies, renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

Special population:

Renal impairment:

There are no pharmacokinetic data available for atazanavir with ritonavir in patients with renal insufficiency.

Hepatic impairment:

Concentrations of atazanavir with ritonavir is expected to increase in patients with moderately or severely impaired hepatic function.

Age/Gender:

There were no clinically important pharmacokinetic differences based on age or gender.

5.3 Preclinical safety data

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

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 the entire rodent studies conducted with ritonavir, but have not been seen in dogs. All thyroid changes were reversible upon discontinuation of ritonavir. 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.

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. The potential for PR prolongation should be considered in cases of overdose.

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

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.

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

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 Salmonella

typhimurium and Escherichia coli, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 Storage condition

Store below 30°C.

Shelf life: Please refer to information on packaging.

6.2 Nature and contents of container

30 Tablets are packed in 120 cc HDPE (High Density polyethylene) bottle. Containers are sealed with 38 mm child resistant closure.

6.3 Manufacturer

Emcure Pharmaceuticals Ltd.

Plot No. P-1 and P-2, Phase II, I.T- B.T Park, M.I.D.C., Hinjawadi, Pune – 411057

Maharashtra state, INDIA

6.4 Date of revision

14.08.2024