SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

AVIRTAZ 150 mg (capsules)

AVIRTAZ 300 mg (capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AVIRTAZ 150 mg:

Each capsule contains:

Atazanavir (as sulphate) equivalent to atazanavir 150 mg

Contains sugar (lactose monohydrate) 84,15 mg

AVIRTAZ 300 mg:

Each capsule contains:

Atazanavir (as sulphate) equivalent to atazanavir 300 mg

Contains sugar (lactose monohydrate) 168,30 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

AVIRTAZ 150 mg

White to pale yellow powder filled in capsules with light sky blue opaque colour cap and light sky blue opaque colour body imprinted with ‘M166’ on both cap and body in black ink.

AVIRTAZ 300 mg

White to pale yellow powder filled in capsules with blue opaque colour cap and light sky blue opaque colour body imprinted with ‘M167’ on both cap and body in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AVIRTAZ is indicated in adults and patients > 12 years of age and body weight of ≥ 40 kg, for the treatment of HIV-1 infection in combination with other antiretroviral medicines.

The efficacy of **AVIRTAZ** has been demonstrated in antiretroviral-naïve and treatment - experienced patients.

AVIRTAZ to be co-administered with a low dose of ritonavir (see section 4.2).

4.2 Posology and method of administration

Posology

Efficacy and safety of **AVIRTAZ** with ritonavir in doses greater than 100 mg once daily have not been established. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and, therefore, is not recommended.

The AVIRTAZ 150 mg and 300 mg capsules are not suitable for patients ≤ 12 years of age and body weight of < 40 kg.

Recommended dosage for treatment naïve and treatment experienced adults and patients > 12 years of age and bodyweight ≥ 40 kg: **AVIRTAZ** 300 mg and ritonavir 100 mg once daily with food.

AVIRTAZ without ritonavir is not recommended for treatment-experienced patients with prior virologic failure.

AVIRTAZ should not be administered to paediatric patients below the age of 3 months due to risk of kernicterus.

Concomitant Therapy:

Efavirenz:

In treatment-naïve patients, it is recommended that **AVIRTAZ** 300 mg and ritonavir 100 mg be taken with efavirenz 600 mg. This should be taken all once daily.

AVIRTAZ without ritonavir should not be co-administered with efavirenz. Dosing recommendations for efavirenz and **AVIRTAZ** in treatment-experienced patients with prior virologic failure have not been established.

Didanosine: It is recommended that all didanosine formulations be administered on an empty stomach and that **AVIRTAZ** be taken with food; therefore, didanosine should be taken 2 hours after **AVIRTAZ** (taken with food) or 1 hour before **AVIRTAZ**.

Tenofovir: When co-administered with tenofovir, it is recommended that **AVIRTAZ** 300 mg be given with ritonavir 100 mg and tenofovir 300 mg, all as single daily dose with food. **AVIRTAZ** without ritonavir should not be co-administered with tenofovir (see section 4.5).

Renal impairment:

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

Special populations

Hepatic Impairment:

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

Pregnancy

During the second and third trimesters of pregnancy:

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

The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicines known to reduce its exposure (e.g. tenofovir disoproxil and an H_2-receptor antagonists).

Postpartum:

Following a possible decrease in atazanavir exposure during the second and third trimester, atazanavir exposures might increase during the first two months after delivery (see section 5.2). Therefore, postpartum patients should be closely monitored for adverse reactions. During this time, postpartum patients should follow the same dose recommendation as for non-pregnant patients, including those for co-administration of medicines know to affect atazanavir exposure (see section 4.5).

Paediatric population

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

The AVIRTAZ 150 mg and 300 mg capsules are not suitable for use in patients ≤ 12 years of age and bodyweight of < 40 kg.

Method of administration

For oral use. The capsules should be swallowed whole.

4.3 Contraindications

- **AVIRTAZ** is contraindicated in patients with known hypersensitivity to atazanavir or any of its ingredients.
- **AVIRTAZ** with ritonavir must not be used in patients with moderate to severe hepatic impairment (see sections 4.2 - *Hepatic impairment*; 4.4 - *Hepatic impairment and toxicity*).
- **AVIRTAZ** is contraindicated when co-administered with medicines that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see section 4.5).
- **AVIRTAZ** is contraindicated when co-administered with medicines that are substrates of the CYP3A4 isoform of cytochrome P450 and have narrow therapeutic windows (e.g. quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5) lomitapide, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.5).
- **AVIRTAZ** is contraindicated in mothers breastfeeding their infants (see section 4.6).
- Voriconazole should not be administered to patients receiving **AVIRTAZ** and ritonavir (see section 4.5).

- **AVIRTAZ** is contraindicated when co-administered with grazoprevir-containing medicines, including elbasvir/grazoprevir fixed-dose combination (see section 4.5).
- **AVIRTAZ** is contraindicated when co-administered with glecaprevir/pibrentasvir fixed-dose combination (see section 4.5).
- **AVIRTAZ** is contraindicated when co-administered with apalutamide (see section 4.5).

Table 1: Medicines that are contraindicated with AVIRTAZ

Medicine Class	**Clinical Comment**
Alpha 1-adrenoreceptor antagonist: alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension.
Antidysrhythmics: quinidine	**AVIRTAZ/ritonavir:** Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Antimycobacterial: rifampicin	Rifampicin substantially decreases plasma concentrations of **AVIRTAZ**, which may result in loss of therapeutic effect and development of resistance.
Calcium Channel Blockers: bepridil	**AVIRTAZ/ritonavir:** Potential for serious and/or life-threatening adverse events.
Ergot Derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
GI Motility Medicine: cisapride	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Herbal Medicines: St. John's wort (*Hypericum perforatum*)	Patients taking **AVIRTAZ** should not use products containing St. John's wort because co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	There may be potential for serious reactions such as myopathy including rhabdomyolysis. (see section 4.5), HMG-CoA Reductase Inhibitors.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Sedative Hypnotics: Orally administered midazolam, triazolam	Potential for increased concentrations of the sedative hypnotic and increased risk of prolonged sedation or respiratory depression.
PDE5 inhibitor: sildenafil	A safe and effective dose in combination with **AVIRTAZ** has not been established for sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil-associated adverse events. For co-administration of sildenafil for the treatment of erectile dysfunction see sections 4.4 and 4.5.

Antineoplastic: irinotecan	**AVIRTAZ** inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Protease Inhibitor: indinavir	**AVIRTAZ** and indinavir are associated with hyperbilirubinaemia. Co-administration of **AVIRTAZ** and indinavir is not recommended (see section 4.8).

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 in accordance with national guidelines.

Co-administration of **AVIRTAZ** with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. **AVIRTAZ** without ritonavir should not be co-administered with efavirenz.

Patients with coexisting conditions

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 **AVIRTAZ** 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 Professional Information (PI) for these medicines (see section 4.8).

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

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

QT prolongation: Dose related asymptomatic prolongations in PR interval with **AVIRTAZ** have been observed in clinical studies. Caution should be used with medicines known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), **AVIRTAZ** should only be used if another appropriate treatment option is not available (see section 5.1). Particular caution should be used when prescribing **AVIRTAZ** in association with medicines 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).

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 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 (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Diabetes mellitus/Hyperglycaemia: New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. In some cases, diabetic ketoacidosis has occurred.

Immune Reconstitution Inflammatory Syndrome (IRIS): Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART), including **AVIRTAZ**. Typically, such reaction presents by paradoxical

deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are *Mycobacterium avium* infection, cytomegalovirus retinitis, *Pneumocystis jiroveci* pneumonia, tuberculosis and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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.

Opportunistic infections: Patients receiving **AVIRTAZ** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others: Patients should be advised that current antiretroviral therapy, including **AVIRTAZ**, does not prevent the risk of transmission of HIV to

others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

PR Interval: AVIRTAZ has the potential to prolong the PR interval as reflected on the electrocardiogram in some patients. **AVIRTAZ** should be used with caution in patients with pre-existing conduction system disease. Caution should be used when co-administering **AVIRTAZ** with medicines known to induce PR interval prolongation.

Rash and associated syndromes: Rashes are usually mild to moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with **AVIRTAZ**. In most patients, rash resolves within 2 weeks while continuing **AVIRTAZ** therapy. **AVIRTAZ** should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome (SJS), erythema multiforme, and toxic skin eruptions including drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in patients receiving **AVIRTAZ**. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. 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.

Hepatic impairment and toxicity: **AVIRTAZ** is metabolised by the liver; caution should be exercised when administering **AVIRTAZ** to patients with hepatic impairment because **AVIRTAZ** concentrations may be increased. (see section 4.2 - ***Hepatic impairment***). Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations.

Cholelithiasis: Cholelithiasis has been reported in patients receiving atazanavir (see section 4.8). Some patients required hospitalisation 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: Cases of nephrolithiasis have been reported during post-marketing surveillance in HIV-infected patients receiving **AVIRTAZ** therapy. Some patients required hospitalisation 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 therapy may be considered.

Hyperbilirubinaemia: Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving **AVIRTAZ**. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving **AVIRTAZ** should be evaluated for alternative aetiologies. No long-term safety data are available for patients experiencing persistent elevations in bilirubin > 5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to **AVIRTAZ** may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for

patients. Dose reduction of **AVIRTAZ** is not recommended since long-term efficacy or reduced doses has not been established.

Indinavir is also associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT and co-administration of these medicines is not recommended (see section 4.5).

Interactions with other medicines

The combination of **AVIRTAZ** with atorvastatin is not recommended (see section 4.5).

Co-administration of **AVIRTAZ** with nevirapine or efavirenz (without ritonavir) is not recommended (see section 4.5).

Atazanavir is metabolised principally by CYP3A4. Co-administration of **AVIRTAZ** and medicines that induce CYP3A4 is not recommended (see sections 4.3 and 4.5).

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

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

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

Concomitant use of **AVIRTAZ**/ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

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

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

Co-administration of **AVIRTAZ** with proton pump inhibitors is not recommended (see section 4.5).

Co-administration of atazanavir 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).

Lactose: AVIRTAZ contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

AVIRTAZ is metabolised in the liver by the cytochrome P450 enzyme system and is an inhibitor of CYP3A4 (cytochrome P450 3A4).

Co-administration of **AVIRTAZ** and medicines primarily metabolised by CYP3A4 (calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors) may result in increased plasma concentrations of the other medicine that could increase or prolong both its therapeutic and adverse effects. Therefore, atazanavir is contraindicated with medicines that are substrates of CYP3A4 and have a narrow therapeutic index: (e.g. quetiapine, lurasidone, alfuzosin, astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil, triazolam, midazolam administered orally (for caution on parenterally administered midazolam) lomitapide, and ergot alkaloids, particularly, ergotamine, dihydroergotamine, ergonovine, methylergonovine) (see section 4.3).

Co-administration of **AVIRTAZ** and medicines that induce CYP3A4, such as rifampicin, may decrease **AVIRTAZ** plasma concentrations and reduce its therapeutic effect. Co-administration of **AVIRTAZ** and medicines that inhibit CYP3A4 may increase **AVIRTAZ** plasma concentrations.

The magnitude of CYP3A4-mediated interactions (effect on **AVIRTAZ** or effect on co-administered medicine) may change when **AVIRTAZ** is co-administered with ritonavir, a potent CYP3A4 inhibitor.

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. The prescribing information for ritonavir should be consulted for information on interactions with ritonavir.

Hepatitis antiviral medicines:

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

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

Co-administration of atazanavir with voxilaprevir- containing medicines is expected to increase the concentration of voxilaprevir. Co- administration of atazanavir with voxilaprevir-containing regimens is not recommended.

Caution should be used when co-administering **AVIRTAZ** with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, verapamil). (see section 4.8).

Inhaled beta-2 agonists: salmeterol: Concomitant use of salmeterol and **AVIRTAZ** may result in increased cardiovascular adverse events associated with salmeterol. Co-administration of salmeterol and **AVIRTAZ** is not recommended.

Alteration in dose of regimen of the following medicines may be recommended based on medicine interaction studies or predicted interactions:

HIV Antiviral medicines:

Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Didanosine: Co-administration of didanosine buffered tablets and **AVIRTAZ** markedly decreased exposure to **AVIRTAZ** (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Co-administration with **AVIRTAZ** did not alter exposure to didanosine. Administration of the enteric-coated formulation of didanosine with **AVIRTAZ** or atazanavir/ritonavir and a light meal decreased exposure to didanosine. (see section 4.2 – ***Concomitant Therapy***).

Stavudine: The co-administration of stavudine with atazanavir is not expected to significantly alter the exposure of stavudine.

Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Tenofovir: Exposure to **AVIRTAZ** is decreased when tenofovir is co-administered with **AVIRTAZ** (see 4.2 **Posology and method of administration" – *Concomitant Therapy***). **AVIRTAZ** increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving **AVIRTAZ** and tenofovir should be monitored for tenofovir-associated adverse events.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Efavirenz: Exposure to **AVIRTAZ** is decreased when efavirenz is co-administered with **AVIRTAZ**. Co-administration of **AVIRTAZ** with efavirenz is not recommended. **AVIRTAZ** should not be co-administered with efavirenz to treatment-experienced patients.

Nevirapine: Nevirapine, an inducer of CYP3A4, decreases atazanavir exposure. There is a potential risk for nevirapine associated toxicity due to the increased nevirapine exposure. Do not co-administer **AVIRTAZ** with nevirapine.

The co-administration of **AVIRTAZ**/ritonavir with zidovudine and lamivudine or with abacavir is not expected to significantly alter the exposure of the co-administered medicines.

Protease Inhibitors:

Saquinavir (soft gelatin capsules): Exposure to saquinavir is increased when it is co-administered with **AVIRTAZ**. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.

Ritonavir: Exposure to **AVIRTAZ** is increased when ritonavir is co-administered with **AVIRTAZ** (see section 4.2).

Indinavir: **AVIRTAZ** and indinavir are associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition UGT. Co-administration of **AVIRTAZ** or indinavir is not recommended.

Other protease inhibitors:

Although not studied, the co-administration of **AVIRTAZ** plus ritonavir with other protease inhibitors would be expected to increase exposure to the other protease inhibitors and is not recommended.

Integrase Inhibitors:

Raltegravir: No dose adjustment required for raltegravir.

Other medicines:

Antacids and buffered medicines: Reduced plasma concentrations of **AVIRTAZ** may result if antacids, including buffered medicines, are administered with **AVIRTAZ**. **AVIRTAZ** should be administered 2 hours before or 1 hour after these medicines.

Alpha 1-adrenoreceptor antagonist:

Alfuzosin: Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir. Co-administration of alfuzosin with atazanavir is contraindicated (see section 4.3).

Antidysrhythmic:

Amiodarone, lidocaine (systemic), quinidine: Concentrations may be increased when co-administered with **AVIRTAZ**. Caution is warranted, and therapeutic concentration monitoring

is recommended when available. Quinidine is contraindicated when **AVIRTAZ** is co-administered with ritonavir.

Anticoagulants:

Direct-acting oral anticoagulants (DOACs)

Apixaban, rivaroxaban, dabigatran: Potential for increased apixaban, rivaroxaban and dabigatran concentrations which can result in a higher risk of bleeding. Co-administration of apixaban, rivaroxaban or dabigatran and atazanavir with ritonavir is not recommended.
Edoxaban: Potential for increased edoxaban concentrations which can result in a higher risk of bleeding. Exercise caution when edoxaban is used with atazanavir. Please refer to the edoxaban professional information sections 4.2 and 4.5 for appropriate edoxaban dosage recommendations for co-administration.

Vitamin K antagonists

Warfarin: Co-administration with **AVIRTAZ** has the potential to produce serious and/or life-threatening bleeding due to increased exposure to warfarin and has not been studied. It is recommended that INR (International Normalised Ratio) be monitored.

Antiplatelets:

Ticagrelor – Co-administration of atazanavir with ticagrelor is not recommended due to potential increase in the antiplatelet activity of ticagrelor.
Clopidogrel – Co-administration of atazanavir with clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
Prasugrel - No dose adjustment is needed when prasugrel is co-administered with atazanavir (with or without ritonavir).

Antidepressants:

Tricyclic antidepressants: Co-administration of tricyclic antidepressants with **AVIRTAZ** has the potential to produce serious and/or life-threatening adverse events due to increased exposure to these medicines and has not been studied. Concentration monitoring of these medicines is recommended if they are used concomitantly with **AVIRTAZ**.

Trazodone: Concomitant use of trazodone and **AVIRTAZ** with or without ritonavir may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as **AVIRTAZ**, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals:

Ketoconazole, itraconazole: Ketoconazole and itraconazole should be used cautiously with **AVIRTAZ** and ritonavir.

Voriconazole: Voriconazole should not be administered to patients receiving **AVIRTAZ** and ritonavir.

Fluconazole: No dosage adjustments are needed for fluconazole and atazanavir.

Antimycobacterials:

Rifabutin: Exposure to rifabutin is increased when it is co-administered with **AVIRTAZ**. A rifabutin dose reduction of up to 75 % (e.g. 150 mg every other day or 3 times per week) is recommended. Increased monitoring for adverse reactions (including neutropenia and uveitis) is warranted in patients receiving the combination of rifabutin and **AVIRTAZ** with or without ritonavir. Further dosage reduction of rifabutin may be necessary.

Rifampicin: The combination of rifampicin and atazanavir is contraindicated (see section 4.3).

Calcium Channel Blockers:

Diltiazem: Exposure to diltiazem and a metabolite, desactyl-diltiazem, is increased when diltiazem is co-administered with **AVIRTAZ**. A dose reduction of diltiazem by 50 % should be considered, and electrocardiogram monitoring is recommended.

Bepridil: Atazanavir should not be used in combination with medicines that are substrates of CYP3A4 and have a narrow therapeutic index. Co-administration with bepridil is contraindicated (see section 4.3).

Other calcium channel blockers, such as felodipine, nifedipine, nicardipine and verapamil: Caution is warranted. Dose titration of the calcium channel blocker should be considered. Electrocardiogram monitoring is recommended.

Erectile Dysfunction medicines:

Phosphodiesterase (PDE5) inhibitors:

Sildenafil, tadalafil, vardenafil: Co-administration of protease inhibitor with a PDE5 inhibitor is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in PDE5 inhibitor-associated adverse events (including hypotension, visual changes, and priapism). Use with caution and monitor for adverse events. Use of sildenafil for the treatment of pulmonary arterial hypertension is contraindicated with **AVIRTAZ** (see section 4.3).

Proton-pump Inhibitors: **AVIRTAZ** co-administered with proton pump inhibitors results in a substantial decrease in atazanavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Plasma concentrations of atazanavir were substantially decreased when **AVIRTAZ** 300 mg/ritonavir 100 mg once daily was administered with omeprazole 20 mg once daily. Doses of omeprazole exceeding 20 mg daily (or comparable dose of an alternative proton-pump inhibitor) are not recommended.

H_2-Receptor Antagonists: Plasma concentrations of atazanavir were substantially decreased when **AVIRTAZ** 300 mg with ritonavir 100 mg once daily was administered with food at least 2 hours before and at least 10 hours after a dose of an H_2-receptor antagonist.

In treatment-experienced patients, the total daily dose of the H_2-recptor antagonist should not exceed a dose comparable to famotidine 40 mg. In these patients, **AVIRTAZ** 300 mg with ritonavir 100 mg should be administered once daily with food at least 2 hours before and at least 12 hours after the H_2-receptor antagonist at a single daily dose comparable to famotidine 40 mg. Alternatively, **AVIRTAZ** 300 mg with ritonavir 100 mg once daily with food may be administered simultaneously with, or at least 2 hours before and at least 10 hours after, a dose of an H_2-receptor antagonist not to exceed a dose comparable to famotidine 20 mg administered once or twice daily.

Lipid modifying medicines:

HMG-CoA Reductase Inhibitors:

Simvastatin, lovastatin: Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with atazanavir may result in increased concentrations. Co-administration of simvastatin or lovastatin with atazanavir is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see section 4.3).

Atorvastatin: Exposure to atorvastatin may be increased when it is co-administered with **AVIRTAZ**. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including **AVIRTAZ**, are used in combination with atorvastatin. Caution should be exercised (see section 4.3, ***Table 1 Medicines that are contraindicated with AVIRTAZ***).

Pravastatin, fluvastatin: Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9. Caution should be exercised.

Other lipid-modifying medicines:

Lomitapide: Lomitapide is highly dependent on CYP3A4 for metabolism and co-administration with atazanavir with ritonavir may result in increased concentrations. Co-administration of lomitapide and atazanavir with ritonavir is contraindicated due to a potential risk of markedly increased transaminase levels and hepatotoxicity (see section 4.3).

Antineoplastics and immunosupressants:

Antineoplastics:

Apalutamide: Co administration with atazanavir (with or without ritonavir) is contraindicated due to the potential for decreased atazanavir and ritonavir plasma concentration with subsequent loss of virologic response and possible resistance to the class of protease inhibitors (see section 4.3). In addition, serum concentrations of apalutamide may be increased when co-administered with atazanavir/ritonavir, resulting in the potential for serious adverse events including seizure.

Encorafenib, ivosidenib: Avoid co-administration of encorafenib or ivosidenib with atazanavir (with or without ritonavir) due to potential for increase in encorafenib or ivosidenib plasma concentrations and subsequent risk of serious adverse events such as QT interval prolongation. If co-administration of encorafenib or ivosidenib with atazanavir (with or without ritonavir) cannot be avoided, refer Summary of Product Characteristics of encorafenib or Ivosidenib.

Irinotecan: Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. **AVIRTAZ** is contraindicated when co-administered with irinotecan (see section 4.3).

Immunosuppressants:

Ciclosporin, tacrolimus, sirolimus: Exposure to ciclosporin, tacrolimus, and sirolimus may be increased when co-administered with **AVIRTAZ**. Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with **AVIRTAZ**.

Corticosteroids

Dexamethasone and other corticosteroids (all routes of administration): Co-administration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of atazanavir and development of resistance to atazanavir and/or ritonavir. Alternative corticosteroids should be considered. The mechanism of interaction is CYP3A4 induction by dexamethasone and CYP3A4 inhibition by atazanavir and/or ritonavir. Co-administration with corticosteroids (all routes of administration) that are metabolised by CYP3A, particularly for long term use, may increase the risk for development of systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. The potential benefit of treatment versus the risk of systemic corticosteroid effects should be considered. For co-administration of cutaneous administered corticosteroids sensitive to CYP3A inhibition, consult the Summary of Product Characteristics of the corticosteroid for condition or uses that augment its systemic absorption.

Inhaled/nasal corticosteroids (interaction with ritonavir): In healthy volunteers, ritonavir significantly increased plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of **AVIRTAZ**/ritonavir with fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir was co-administered with inhaled or intranasally administered fluticasone propionate. These effects could also occur with other corticosteroids metabolised via the cytochrome P450 3A pathway, e.g. budesonide. Therefore, concomitant use of **AVIRTAZ**/ritonavir and fluticasone propionate or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use of fluticasone propionate and **AVIRTAZ** (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.

Macrolide Antibiotics:

Clarithromycin: Exposure to clarithromycin is increased when it is co-administered with **AVIRTAZ**. Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50 % should be considered when it is co-administered with **AVIRTAZ**.

Benzodiazepine:

Midazolam: Midazolam and triazolam are extensively metabolised by CYP3A4. Although not studied, co-administration of midazolam or triazolam with **AVIRTAZ** may cause a large increase in the concentration of benzodiazepines. Increases in benzodiazepine concentration are expected to be significantly higher with oral administration of the benzodiazepine, relative to parenteral. Therefore, **AVIRTAZ** should not be co-administered with orally administered midazolam or triazolam (see section 4.3). Caution should be used with co-administration of **AVIRTAZ** and parenteral midazolam. If **AVIRTAZ** is co-administered with parenteral midazolam, a close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised, and dosage adjustment should be considered.

Antipsychotics:

Quetiapine: Co-administration of quetiapine with atazanavir is contraindicated as atazanavir may increase quetiapine- related toxicity. Increased plasma concentrations of quetiapine may lead to coma (see section 4.3).

Lurasidone: Co-administration of lurasidone with atazanavir is contraindicated as this may increase lurasidone-related toxicity (see section 4.3).

Antiepileptics:

Carbamazepine: Atazanavir may increase plasma levels of carbamazepine due to CYP3A4 inhibition. Due to carbamazepine inducing effect, a reduction in atazanavir exposure cannot be ruled out. Carbamazepine should be used with caution in combination with atazanavir. If necessary, monitor carbamazepine serum concentrations and adjust the dose accordingly. Close monitoring of the patient's virologic response should be exercised.

Phenytoin, phenobarbital: Ritonavir may decrease plasma levels of phenytoin and/or phenobarbital due to CYP2C9 and CYP2C19 induction. Due to phenytoin/phenobarbital inducing effect, a reduction in atazanavir exposure cannot be ruled out. Phenobarbital and phenytoin should be used with caution in combination with atazanavir /ritonavir. When atazanavir/ritonavir is co-administered 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: Co-administration of lamotrigine and atazanavir/ritonavir may decrease lamotrigine plasma concentrations due to UGT1A4 induction. Lamotrigine should be used with caution in combination with atazanavir/ritonavir. If necessary, monitor lamotrigine concentrations and adjust the dose accordingly.

Opioids:

Buprenorphine: Concentrations of buprenorphine and norbuprenorphine were increased when buprenorphine was co-administered with **AVIRTAZ**, with or without ritonavir, due to CYP3A4 and UGT1A1 inhibition. Co-administration of **AVIRTAZ** plus ritonavir with buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. There was no significant effect on atazanavir plasma concentration when **AVIRTAZ** plus ritonavir were co-administered with buprenorphine. Co-administration of buprenorphine and **AVIRTAZ** without ritonavir may substantially decrease atazanavir plasma concentrations. **AVIRTAZ** without ritonavir should not be co-administered with buprenorphine.

Methadone: No dosage adjustment is necessary if methadone is co-administered with atazanavir.

Oral Contraceptives:

Ethinylestradiol and norethindrone: Mean concentrations of ethinylestradiol and norethindrone are increased when they are co-administered with **AVIRTAZ**. Decreased HDL or increased insulin resistance may be associated with increased concentrations of norethindrone, particularly in diabetic women. It is recommended that the lowest effective dose of each oral contraceptive component be used. Alternate methods of non-hormonal contraception should be considered when **AVIRTAZ** is taken with ritonavir. Administration of **AVIRTAZ** plus ritonavir with ethinylestradiol and norgestimate decreases the mean concentration of ethinylestradiol by 20 % and increases the mean concentration of 17-deacetyl norgestimate by 68 %, the active metabolite of norgestimate. If an oral contraceptive is administered with **AVIRTAZ** plus ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinylestradiol.

If **AVIRTAZ** is administered without ritonavir, the oral contraceptive should contain no more than 30 µg of ethinylestradiol. Use with caution as the effect of increases in concentration of the progestational medicines are unknown and could increase the risk of acne, dyslipidaemia, and insulin resistance.

Co-administration of **AVIRTAZ** or **AVIRTAZ**/ritonavir with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate, or less than 25 µg of ethinylestradiol have not been studied; therefore, alternative methods of contraception are recommended.

Gonadotropin releasing hormone (GnRH) receptor antagonists:

Elagolix: The mechanism of interaction is anticipated increase in elagolix exposure in the presence of CYP3A4 inhibition by atazanavir and/or ritonavir. Concomitant use of elagolix 200 mg twice daily with atazanavir (with or without ritonavir) for more than 1 month is not recommended due to the potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily with atazanavir (with or without ritonavir) to 6 months.

Kinase inhibitors

Fostamatinib: The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or ritonavir. Concomitant use of fostamatinib with atazanavir (with or without ritonavir) may increase the plasma concentration of R406, the active metabolite of fostamatinib. Monitor for toxicities of R406 exposure resulting in dose related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required.

Herbal medicines:

St. John's wort (Hypericum perforatum): Concomitant use of St. John's wort with atazanavir may be expected to result in significant reduction in plasma levels of atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance (see section 4.3). Co-administration of atazanavir with medicines containing St. John's wort is contraindicated.

Effect on other Cytochrome P450 (CYP) enzymes: Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when **AVIRTAZ** without ritonavir is co-administered with medicines highly dependent on CYP2C8 with narrow therapeutic indices.

4.6 Fertility, pregnancy and lactation

Safe use during pregnancy and lactation has not been established.

Pregnancy

Hyperbilirubinaemia occurred frequently during treatment with **AVIRTAZ**. It is not known whether **AVIRTAZ** administered to the mother during pregnancy will exacerbate physiological hyperbilirubinaemia and lead to kernicterus in neonates and young infants. In the prepartum period, additional monitoring and alternative therapy to **AVIRTAZ** should be considered.

Dosing during Pregnancy and the Postpartum Period

- **AVIRTAZ** should not be administered without ritonavir.
- For pregnant patients, no dose adjustment is required for **AVIRTAZ** with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when **AVIRTAZ** is co-administered with either an H_2-receptor antagonist or tenofovir. There are insufficient data to recommend an **AVIRTAZ** dose for use with both an H_2-receptor antagonist and tenofovir in treatment-experienced women.
    - No dose adjustment is required for postpartum patients. However, patients would be closely monitored for adverse events because atazanavir exposure could be higher during the first 2 months after delivery.

Breastfeeding

It is not known whether **AVIRTAZ** is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in breastfed infants,

mothers receiving **AVIRTAZ** should be instructed not to breastfeed their infants. (see section 4.3).

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

AVIRTAZ may influence the ability to drive and use machines.

AVIRTAZ may cause dizziness, drowsiness and syncope. Patients who experience these adverse effects should be advised not to drive or use machines (see section 4.8).

4.8 Undesirable effects

AVIRTAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicines in controlled clinical trials in adult patients who received **AVIRTAZ** 300 mg once daily plus ritonavir 100 mg once daily.

Summary of safety profile

The more frequent adverse events of any severity with at least a possible relationship to regimens containing **AVIRTAZ** and one or more NRTIs were nausea (20 %), jaundice (13 %), and diarrhoea (10 %). Jaundice was reported within a few days to a few months after the initiation of treatment and resulted in discontinuation of treatment in < 1 % of patients.

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).

Lipodystrophy of moderate intensity or greater, was reported in regimens containing **AVIRTAZ** and one or more NRTIs, as at least possibly related to the regimen, in 5 % of patients.

Tabulated summary of adverse reactions

The following adverse reactions of moderate intensity or greater with at least a possible relationship to regimens containing **AVIRTAZ** and one or more NRTIs have been reported:

Immune system disorders	*Less Frequent:*	allergic reaction, hypersensitivity
Metabolism and nutrition disorders	*Less Frequent:*	anorexia, increased appetite, decreased weight, weight gain
Psychiatric disorders	*Less Frequent:*	anxiety, depression, sleep disorder, insomnia, abnormal dream, disorientation
Nervous system disorders	*Frequent:*	headache
	Less Frequent:	peripheral neurologic symptoms, amnesia, somnolence, dizziness, dysgeusia
Eye disorders	*Frequent:*	Ocular/scleral icterus
Cardiac disorders	*Less Frequent:*	syncope, oedema, palpitations

Vascular disorders	*Less Frequent:*	hypertension
Respiratory, thoracic and mediastinal disorders	*Less Frequent:*	dyspnoea
Gastrointestinal disorders	*Frequent:*	abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
	Less Frequent:	dry mouth, flatulence, gastritis, pancreatitis, stomatitis aphthous, abdominal distension
Hepato-biliary disorders	*Frequent:*	jaundice
	Less Frequent:	hepatitis, hepatosplenomegaly
Skin and subcutaneous tissue disorders	*Frequent:*	rash
	Less Frequent:	alopecia, pruritus, urticaria, erythemia multiforme, toxic skin eruptions, drug rash with eosinophilia and systemic symptoms (DRESS syndrome), angioedema, vasodilation, vesiculobullous rash, eczema, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	*Less Frequent:*	arthralgia, muscle atrophy, myalgia, myopathy

Renal and urinary disorders	*Less Frequent:*	haematuria, pollakiuria, proteinuria, nephrolithiasis, interstitial nephritis, kidney pain, chronic kidney disease
Reproductive system and breast disorders	*Less Frequent:*	gynaecomastia
General disorders and administration site conditions	*Frequent:*	asthenia, fatigue
	Less Frequent:	chest pain, fever, malaise, gait disturbance

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 - Immune Reconstitution Inflammatory Syndrome (IRIS)).

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

Metabolic parameters

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

Rash and associated syndromes

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

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

Laboratory findings:

Adult Patients:

The most frequently reported laboratory abnormality in patients receiving regimens containing **AVIRTAZ** 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).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2 % of patients receiving regimens containing **AVIRTAZ** and one or more NRTIs included: elevated creatine kinase (CK) (7 %), elevated ALT/SGPT (5 %), low neutrophils (5 %), elevated AST/SGOT (3 %), and elevated lipase (3 %). In clinical studies, the observed magnitude of dyslipidaemia was less with **AVIRTAZ** than with comparators.

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

Paediatric patients:

The most common Grade 3 - 4 laboratory abnormalities occurring in paediatric patients were elevation of total bilirubin (≥ 3,2 mg/dl, 58 %), neutropenia (9 %), and hypoglycaemia (4 %). All other Grade 3 – 4 laboratory abnormalities occurred with a frequency of less than 3 %.

Paediatric population:

The safety profile of **AVIRTAZ** in paediatric patients (6 to less than 18 years of age) was comparable to that observed in clinical studies of **AVIRTAZ** in adults.

The most common Grade 2 – 4 adverse events (≥ 5 %, regardless of causality) reported in paediatric patients were cough, fever, jaundice/scleral icterus, rash, vomiting, diarrhoea, headache, peripheral oedema, extremity pain, nasal congestion, oropharyngeal pain, wheezing and rhinorrhoea. Asymptomatic second-degree atrioventricular block was reported in < 2 % of patients.

Other special populations

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

The frequency of treatment-emergent hepatitis or transaminase elevations in co-infected patients was comparable between **AVIRTAZ** and comparator regimens. No differences in frequency of bilirubin elevations were observed.

Post-marketing experience:

The following events have been identified during post approval use of **AVIRTAZ**. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac disorders and vascular disorders: Second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes (see section 4.4).

Metabolism and nutrition disorders: hyperglycaemia, diabetes mellitus (see section 4.4).

Renal and urinary disorders: nephrolithiasis.

Hepatobiliary disorders: cholelithiasis, cholecystitis, cholestasis.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Human experience of acute overdose with **AVIRTAZ** is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. These events resolved spontaneously. At high doses that lead to high medicine exposure, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations, may be observed.

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

5 PHARMACOLOGICAL PROPERTIES

A 20.2.8 Antiviral Agents.

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

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Absorption

No substantial differences were observed between the pharmacokinetics of healthy adult volunteers and in HIV-infected patients.

Administration of atazanavir sulphate with food enhances bioavailability and reduces pharmacokinetic variability.

Distribution

Atazanavir is 86 % bound to human serum proteins.

Biotransformation and Elimination

Atazanavir is principally metabolised by the CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites.
The mean elimination half-life of atazanavir in healthy volunteers and HIV-infected adult patients was approximately 7 hours.

Microbiology:

Resistance in vitro:

Atazanavir susceptibility was evaluated in clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. There was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was

retained among isolates resistant to 1 – 2 protease inhibitors, despite the presence of primary substitutions associated with resistance to protease inhibitors.

Resistance in vivo:

Distinct resistance patterns appeared in atazanavir-containing regimens depending on whether patients had previously received protease inhibitor therapy and whether their study treatment utilised un-boosted atazanavir as the only protease inhibitor or, atazanavir plus ritonavir.

Treatment-experienced patients

Approximately 80 % and 100 % of atazanavir-resistant isolates from experienced patients treated with atazanavir or the combination of atazanavir plus saquinavir, respectively, showed no evidence of the emergence of the I50L substitution, instead displaying decreased susceptibility to multiple protease inhibitors, which coincided with the accumulation of several additional amino acid substitutions, including I84V.

In studies of treatment-experienced patients treated with ATV/RTV most ATV-resistant isolates from patient's who experienced virologic failure through 48 weeks developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions (> 10 % frequency) to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg daily (together with tenofovir and NRTI) included L10F, K20I/M/V, V32I, M36I/L, M46I/L, I54/V, A71V/T/I, G73S/T/C, and V82A/T/L. Other substitutions that developed an ATV/RTV treatment including L24I, L33F/I/V, G48V, I50L/V, I84V, and L90M occurred in less than 10 % of patient isolates.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone, lactose monohydrate and magnesium stearate.

Capsule shell: FD&C Blue # 2, gelatin and titanium dioxide.

Capsule shell imprints (edible ink): black iron oxide and shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original container.

Keep the bottle tightly closed.

Keep the bottle in the carton until required for use.

6.5 Nature and contents of container

AVIRTAZ 150 mg is packed in a round, wide mouth, white HDPE bottle with white opaque screw cap with induction sealing liner. Packed in an outer carton in pack sizes of 28', 30's & 100's.*

AVIRTAZ 300 mg is packed in a round, wide mouth, white HDPE bottle with white opaque screw cap with induction sealing liner. Packed in an outer carton in pack sizes of 28's, 30's & 100's.*

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando,

Kempton Park,

Gauteng, 1601

Tel.: +2711 451 1300

8 REGISTRATION NUMBER(S)

Avirtaz 150 mg: 46/20.2.8/0970

Avirtaz 300 mg: 46/20.2.8/0971

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 June 2021

10 DATE OF REVISION OF THE TEXT

30 March 2026