PROFESSIONAL INFORMATION FOR

ATAZANAVIR AND RITONAVIR 300/100 mg (FILM COATED TABLETS)

WARNING:
CO-ADMINISTRATION OF RITONAVIR, AS IN TARITO, WITH CERTAIN NON-SEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTI-DYSRHYTMICS OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF THE RITONAVIR COMPONENT OF TARITO ON THE HEPATIC METABOLISM OF THESE MEDICINES. (SEE SECTION 5.2 AND SECTION 4.4)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TARITO 300/100 mg FILM COATED TABLETS.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains atazanavir sulphate equivalent to atazanavir 300 mg and ritonavir 100 mg.

Contains sugar: lactose monohydrate 104,91 mg.

For the full list of excipients, see **Section 6.1**.

3. PHARMACEUTICAL FORM

Film coated tablets.

TARITO are yellow coloured capsule shaped, biconvex, film coated tablets debossed with “SVN” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TARITO is indicated in combination with other anti-retroviral medicines for the treatment of HIV-1, in both treatment-naïve and treatment experienced patients, weighing 40 kg or more.

4.2 Posology and method of administration

Posology:

The recommended adult dose of TARITO in treatment naïve and treatment experienced patients is one tablet (300/100 mg) once daily, with food.

Special populations

Paediatric population:

The recommended paediatric dose of TARITO for patients with a body weight of 40 kg or more (≥40 kg) is one tablet (300/100 mg) once daily with food.

TARITO should not be administered to paediatric patients weighing less than 40 kg.

Concomitant Therapy

Didanosine

TARITO should be taken 2 hours before didanosine as it needs to be taken with food while didanosine is best taken on an empty stomach.

Tenofovir

The recommended dose of TARITO in combination with tenofovir 300 mg should be given as a single daily dose, with food.

Renal Impairment

In patients with renal impairment, including those with severe renal impairment, not managed by haemodialysis, no dosage adjustment of TARITO is required.

TARITO should not be administered to treatment experienced patients with severe renal impairment managed with haemodialysis.

Hepatic Impairment

There is no data on the use of TARITO in patients with hepatic impairment. TARITO should be used with caution in patients with mild hepatic impairment **(**see **section 4.4).**

TARITO should not be used in patients with moderate (Child-Pugh B, score 7-9) or severe hepatic impairment (Child-Pugh C, score 10-15) **(**see **section 4.3).**

TARITO should not be used in patients with decompensated liver disease.

Method of administration

TARITO is for oral administration and should be swallowed whole.

TARITO should be taken with food.

4.3 Contraindications

TARITO is contraindicated:

- In patients with known hypersensitivity to atazanavir, ritonavir, or any of its excipients, **(**see **section 6.1)**
- In patients with moderate (Child-Pugh B, score 7-9) or severe hepatic impairment (Child-Pugh C, score 10-15) or decompensated liver disease **(**see **section 4.4)**.
- In treatment experienced patients with severe renal impairment managed with haemodialysis,
- In patients with second or third degree heart block,

- Pregnancy and mothers breastfeeding their infants, (see Fertility, pregnancy and lactation, **section 4.6**),
- Voriconazole should not be administered to patients being treated with TARITO**,**
- In patients on anti-tuberculosis treatment regimens containing rifampicin **(**see **section 4.5),**
- 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 interactions in the table below.

  Ritonavir, an active constituent of TARITO, is a potent inhibitor of many cytochrome P450 mediated biotransformation. Ritonavir has been shown or is expected to largely increase plasma concentrations of medicines that are metabolised by cytochrome P450.

- **Table 1: Concomitant use of TARITO and the following medicines are contraindicated:**

Medicine class	**Contraindicated medicine within the class**	**Clinical comments**
Alpha1-adrenoreceptor antagonist	Alfuzosin hydrochloride	Potential for hypotension.
Analgesics	Pethidine, Piroxicam, Propoxyphene	Increased levels of these may result in increased risk of serious respiratory depression or haematologic abnormalities.
Antianginal	Ranolazine	Increased plasma concentrations of

		ranolazine may increase the potential of serious and/or life-threatening reactions (**see section 4.5**).
Anticancer	Ventoclax	Increased plasma concentrations could result in increased risk of tumour lysis syndrome **(**see **section 4.5).**
Antidysrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine, encainide and digoxin	Potential for cardiac dysrhythmias.
Antibiotics	Fusidic Acid	Increased plasma levels of fusidic acid as well as ritonavir which is an active constituent of TARITO.
Antifungal	Voriconazole	Significant decreases in voriconazole plasma concentrations may lead to loss of antifungal response.
Antigout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal or hepatic impairment.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine, thereby, increasing the risk of serious dysrhythmias from these medicines.
Antimycobacterial	Rifampicin,	Rifampicin may decrease plasma concentrations of atazanavir which is an

		active substance of TARITO. This may result in reduced therapeutic effect and resistance.
	Rifabutin	TARITO may increase concentrations of rifabutin leading to increased risk of adverse effects.
Antipsychotic/Neuroleptics	Blonanserin,	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin.
	Lurasidone,	Increased concentrations of lurasidone may increase potential for serious and or life-threatening reactions.
	Clozapine, Pimozide,	Increased concentrations of clozapine and pimozide may increase the risk of serious haematologic abnormalities.
	Quetiapine	Increased concentrations of quetiapine may lead to coma.
Calcium Channel Blockers	Bipridil	Potential for serious and/or life-threatening adverse events.
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine and methylergonovine	Increased concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia of the extremities and other

		tissues.
Gastrointestinal motility medicine	Cisapride	Potential for cardiac dysrhythmias.
Herbal products	St John's Wort (*Hypericum perforatum*)	Co-administration may lead to a decrease in atazanavir and ritonavir levels, and to loss of virologic response and possible resistance to atazanavir ritonavir or to the class of protease inhibitors.
HMG-CoA reductase inhibitors	Lovastatin and simvastatin	Increased concentrations of lovastatin and simvastatin therefore increasing potential for myopathy including rhabdomyolysis.
Long acting beta-adrenoreceptor agonist	Salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	May result in increased concentrations of lomitapide.
Neuroleptic	Pimozide	Potential for cardiac dysrhythmias.
PDE5 inhibitors	Sildenafil (when used for treatment of pulmonary arterial hypertension), see **section 4.4** and **section 4.5** for co-	Increased potential for sildenafil associated adverse events (which include hypotension and syncope).

	administration in patients with erectile dysfunction. Avanafil, Vardenafil	 Potential increase in concentrations of avanafil and vardenafil.
Protease inhibitors	Indinavir	Increased risk of hyperbilirubinemia when administered with TARITO.
Sedative/ hypnotics	Midazolam, triazolam, clorazepate, diazepam, estazolam, flurazepam.	Potential of increases in these highly metabolised sedatives and hypnotics resulting in the risk of prolonged or increased sedation or respiratory depression.
Antineoplastic	Irinotecan	Atazanavir which is an active of TARITO inhibits UGT and may interfere with the metabolism of irinotecan, resulting in toxicity.

4.4 Special warnings and precautions for use

Although the safety and efficacy of atazanavir and ritonavir have been established when administered concomitantly as separate medicines, the safety and efficacy of atazanavir and ritonavir administered in a fixed dose combination tablet have not been established in clinical studies.

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

Allergic reaction

Allergic reactions such as urticaria, skin eruptions, bronchospasm, angioedema, anaphylaxis, and Stevens-Johnson syndrome (SJS) have been reported.

Rash

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with TARITO. In most patients, the rash resolves within 2 weeks while continuing therapy, but TARITO should be discontinued if a severe rash develops.

Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions including drug rash, eosinophilia, and systemic symptoms (DRESS) have also been reported in patients using TARITO. If the patient has developed SJS or DRESS associated with the use of TARITO, TARITO may not be restarted

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy, such as TARITO, has been associated with body fat redistribution 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.

Hepatic impairment and toxicity

Atazanavir as in TARITO is extensively metabolised by the liver; therefore, caution should be exercised when administering TARITO to patients with hepatic impairment (pre-

existing mild liver disease, liver enzyme abnormalities or hepatitis) as it may result in increased concentration of atazanavir (see **section 4.2**).

The safety of TARITO in patients with significant underlying liver disorders has not been established (see **section 4.2**).

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. Increased AST/ALT monitoring should be considered in patients during the first three months of treatment. Patients with underlying Hepatitis B or C may experience serious and potentially fatal hepatic adverse effects.

There have been reports of hepatic dysfunction, including fatalities, particularly in patients taking multiple concomitant medicines and/or with advanced AIDS. Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice have been reported in patients receiving ritonavir alone or in combination with other anti-retroviral medicines.

TARITO is contraindicated in patients with moderate to severe hepatic insufficiency (see **section 4.3**).

Haemophilia

Events of increased bleeding, including spontaneous skin haematomas and haemoarthrosis, in patients with haemophilia type A and B treated with protease inhibitors such as TARITO have been reported. In some patients an additional factor VIII was given. Treatment with the protease inhibitor is mostly continued or re-introduced.

Renal impairment

TARITO is not recommended in patients undergoing haemodialysis. (see **section 4.3**)

Nephrolithiasis

Cases of nephrolithiasis have been reported during post-marketing surveillance in HIV-infected patients receiving atazanavir therapy. If signs and symptoms of nephrolithiasis occur while a patient is being treated with TARITO, temporary interruption or discontinuation of therapy may be considered.

Pancreatitis

Pancreatitis has been reported in in patients receiving ritonavir, which is an active constituent of TARITO, including those who developed hypertriglyceridemia. **Fatalities have been observed**. Patients with advanced HIV disease may be at an increased risk of pancreatitis and hypertriglyceridemia. Pancreatitis should be considered if clinical symptoms (like nausea vomiting, and/or abdominal pain) or abnormal laboratory values (such as increased serum lipase or amylase) indicative of pancreatitis occur. Patients with these signs should be monitored for pancreatitis and therapy should be discontinued if pancreatitis has been diagnosed.

Diabetes mellitus/ hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported in HIV-infected patients receiving protease inhibitor therapy like TARITO. Some patients require either initiation or dose adjustment of insulin or oral hypoglycaemic medicine for the treatment of these events. In some instances, diabetic ketoacidosis has occurred. Hyperglycaemia is known to persist in some patients who discontinued protease inhibitor therapy.

Patients with chronic diarrhoea or malabsorption

The relatively high frequency if diarrhoea during treatment with TARITO may compromise the absorption due to reduced compliance that may occur. Persistent vomiting and/or diarrhoea may also compromise renal function therefore patients with renal impairment should be monitored.

PR interval prolongation

TARITO may cause PR interval prolongation of the electrocardiogram first-degree atrioventricular block in some patients**.** TARITO should be used with caution in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong PR interval (e.g. verapamil). (see **section 5.2**)

Cholelithiasis

Cholelithiasis has been reported in patients being treated with atazanavir, which is an active ingredient in TARITO. If signs and symptoms of cholelithiasis occur, temporary interruption or discontinuation of treatment may be necessary.

Chronic kidney disease

Chronic kidney disease has been reported in patients treated with HIV regimens containing atazanavir and ritonavir. Patients on TARITO should therefore be constantly monitored for kidney function throughout the duration of their treatment.

Immune Reconstitution Inflammatory Syndrome (IRIS)

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). 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 tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, pneumocystis jirovecii (carinii) pneumonia, Mycobacterium avium infection, 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 and autoimmune hepatitis) 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 aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving TARITO should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore 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 TARITO, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Hyperbilirubinemia

Reversible increases in indirect (unconjugated) bilirubin related to inhibition of UDP glucuronosyl transferase (UGT) have been reported in patients receiving TARITO. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving TARITO should be evaluated for alternative aetiologies. Long term safety data are not available for patients experiencing persistent elevations in bilirubin more than 5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to TARITO should be considered in patients with jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients.

Weight and metabolic parameters

The use of antiretroviral therapy may result in an increase in weight, blood lipid and glucose levels. Patients being treated with TARITO should be advised to lead a healthy lifestyle and their lipid and glucose levels should be monitored

Resistance/ cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of products containing ritonavir such as TARITO, following loss

of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect TARITO therapy will have on the activity of concordantly or subsequently administered protease inhibitors.

Laboratory tests

Ritonavir, an active ingredient in TARITO, has been associated with alterations in triglycerides, ALT, AST, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating TARITO therapy and at periodic intervals or if any clinical signs or symptoms occur during treatment. Medical practitioners should refer to complete product information of nucleoside analogues for comprehensive information on laboratory test alterations related to these products.

Corticosteroids

Concomitant use of medicines containing ritonavir as in TARITO with fluticasone propionate can result in significant increases in fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects such as Cushing's syndrome and adrenal suppression have been reported when ritonavir as in TARITO has been co-administered with inhaled or intranasally administered fluticasone propionate. Similar observations were made when products containing ritonavir were concomitantly administered with other inhaled corticosteroids that are metabolised similarly to fluticasone (e.g. budesonide). Caution should be exercised when TARITO is co-administered with any of these inhaled or intranasally administered glucocorticoids.

Salmeterol

The concomitant use of products containing atazanavir with salmeterol is not recommended as it may result in increased cardiovascular adverse events. **(**see **section 4.3)**

Hormonal contraceptives

The safety of TARITO with contraceptives containing progesterone other than norgestimate has not been studied and therefore co-administration should be avoided.

Barrier or other non-hormonal contraceptives should be considered when administering TARITO as ritonavir may reduce the effect and change the uterine bleeding profile when administered with ethinyl-estradiol containing contraceptives.

PDE5 inhibitors

Concomitant use of TARITO with PDE5 inhibitors is expected to increase their concentrations and may result in increased associated adverse events such as hypotension, visual changes, and priapism.

Concomitant use of TARITO with sildenafil, tadalafil or vardenafil is contraindicated in patients with pulmonary hypertension. **(**see **section 4.3)**

HMG-CoA reductase inhibitors

Caution must be exercised, and reduced doses should be considered if TARITO is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Concomitant use of TARITO with simvastatin and lovastatin is contraindicated as they are highly dependent on CYP3A for metabolism therefore causing an increased risk of myopathy and rhabdomyolysis. **(**see **section 4.3)**

Herbal products

Patients who are being treated with TARITO should not use products containing St. John's Wort (hypericum perforatum) as co-administration may reduce plasma levels of TARITO. This may result in loss of therapeutic effect and the development of resistance. (see **section 4.3)**

Digoxin

Caution should be used when prescribing TARITO to patients on digoxin as ritonavir is expected to increase plasma levels of digoxin. This increase may however lessen over time.

Patients who are already taking digoxin when TARITO is introduced should be reduced to one half of the patients' normal digoxin dose.

Patients who are already taking TARITO when digoxin is introduced should be introduced more gradually than usual and digoxin levels should be monitored intensively.

Trazodone

Trazodone is CYP3A4 substrate and its co-administration with medicines containing ritonavir is expected to increase plasma trazodone concentrations thereby causing effects such as nausea, dizziness, hypotension, and syncope.

Rivaroxaban

The co-administration of TARITO with rivaroxaban should be avoided unless there is no safer appropriate anticoagulant available or has failed as there is an increased risk of bleeding.

Bedaquiline

The combination of TARITO may increase levels of bedaquiline resulting in an increase of adverse events associated with its use. Co-administration should therefore be avoided.

Other ARV medicines

The combination of TARITO with nevirapine or efavirenz is not recommended.

Geriatric use

Safety and efficacy have not been established in the elderly.

Paediatric population

Caution should be exercised when administering TARITO to paediatric patients taking medicines that cause PR interval prolongation.

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

TARITO should only be taken by paediatric patients with a body weight of 40 kg or more.

Lactose

TARITO contains lactose which may influence the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TARITO.

4.5 Interaction with other medicines and other forms of interaction

Atazanavir is metabolised in the liver by the cytochrome P450 enzyme system and is an inhibitor of CYP3A4.

Ritonavir has a high affinity for several cytochrome P450 isoforms with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2 and CYP2E1. There is evidence that ritonavir may induce glucuronosyl transferase, CYP1A2, CYP2C9 and CYP2C19 enzymes

Co-administration of TARITO and medicines primarily metabolised by CYP3A (calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors) may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. Co-administration of TARITO with medicines that increase CYP3A4 activity such as rifampicin, phenobarbitone, carbamazepine, dexamethasone, phenytoin and rifabutin may reduce TARITO concentrations and its therapeutic effect.

Caution is recommended when co-administering TARITO with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, and verapamil) **(**see **section 4.8)**.

Cardiac and neurologic events have been reported when ritonavir-containing medicines such as TARITO are co-administered with disopyramide, mexiletine, nefazodone or fluoxetine. The possibility of interaction cannot be excluded.

List of medicines that interact with TARITO:

Anti-retroviral medicines:

Nucleoside reverse transcriptase inhibitors (NRTI's)

Didanosine

Co-administration of the enteric-coated formulation of didanosine with TARITO and a light meal could lead to decreased exposure to didanosine.

Tenofovir

Co-administration of TARITO and tenofovir decreases TARITO exposure and increases tenofovir plasma concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving TARITO and tenofovir should be monitored for tenofovir-associated adverse events.

Non-nucleotide reverse transcriptase inhibitors (NNRTI's)

Efavirenz

TARITO exposure is reduced by co-administration with efavirenz.

Co-administration of TARITO with efavirenz is not recommended.

TARITO should not be co-administered with efavirenz to treatment-experienced patients.

Nevirapine

Co-administration of TARITO with nevirapine is not recommended because nevirapine (an inducer of CYP3A4) has potential to lower TARITO exposure. There is also a potential for Nevirapine toxicity which comes with an increase in nevirapine exposure.

Protease inhibitors

Saquinavir (soft gel capsules)

Exposure to saquinavir is increased when it is co-administered with TARITO. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.

Other protease inhibitors

Although it has not been studied, Co-administration of TARITO with other protease inhibitors is not recommended due to an expected risk of increased exposure to the other protease inhibitors.

Co-administration of TARITO with indinavir may increase serum concentrations of indinavir. There are limited data on the use of this combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equivalent to or greater than 800 mg twice daily are given with TARITO. Adequate hydration and monitoring of patients is recommended.

Antacids and buffered medications

Reduced plasma concentrations of TARITO may occur if antacids,

including buffered medications, are co-administered with it.

TARITO should be administered 2 hours before or 1 hour after these medicines.

Anti-dysrhythmics

Concentrations of Amiodarone, and Lidocaine(systemic), may be increased by co-administration with TARITO, therefore caution and therapeutic concentration monitoring is recommended.

Anti-coagulants

Concomitant use of Warfarin with TARITO may lead to serious or life-threatening bleeding due to increased exposure to warfarin. Concomitant use of warfarin and TARITO is contraindicated unless no safer anticoagulant is available or has failed. In these cases, caution is advised, and the INR (international normalised ratio) must be monitored frequently.

Anti-cancer

Vincristine and vinblastine*:* Concomitant use with ritonavir, contained in TARITO, may increase vincristine and vinblastine concentrations, leading to increased incidence of adverse events.

Anti-depressants

Concomitant use of Tricyclic anti-depressants with TARITO has not been studied, however, serious, or life-threatening adverse events may occur due to increased exposure to these medicines. Therefore, monitoring of the tricyclic anti-depressant being used concomitantly with TARITO is recommended.

Concomitant use of Trazodone with TARITO may increase trazodone plasma concentrations. Adverse events such as nausea, dizziness, hypotension and syncope may occur. Caution is advised when using trazodone with a CYP3A4 inhibitor such as TARITO and a lower dose of trazodone must be considered.

Co-administration of TARITO with bupropion is expected to result in a decrease in bupropion concentrations.

Concomitant use of buspirone with TARITO is expected to substantially increase buspirone levels.

Antifungals

Caution must be exercise when using TARITO with itraconazole and ketoconazole.

Anti-mycobacterials

Co-administration of rifabutin and TARITO raises plasma concentrations of rifabutin. Rifabutin dose reduction by up to 75 % (e.g. 150 mg every other day or 3 times per week)

is recommended. Adverse reactions should be monitored closely in patients being treated with rifabutin and TARITO simultaneously.

Calcium channel blockers

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

Caution is warranted when using TARITO with other calcium channel blockers such as felodipine, nifedipine, nicardipine and verapamil. Dose titration of the calcium channel blocker should be considered. Electrocardiogram monitoring is recommended.

Medicines for erectile dysfunction

Concomitant use of Phosphodiesterase (PDE5) inhibitors including sildenafil, tadalafil and vardenafil with a protease inhibitor like TARITO is expected to significantly increase the PDE5 inhibitors' concentrations and may result in an increase in the associated adverse events **(**see **section 4.4)**. PDE5 inhibitors are contraindicated in patients with pulmonary hypertension.

Proton pump inhibitors

Co-administration of medicines containing atazanavir such as TARITO with proton pump inhibitors such as omeprazole could result in reduction of atazanavir plasma concentrations which may result in loss of therapeutic effect and possible development of resistance. Doses of omeprazole exceeding 20 mg daily are not recommended.

H_2-receptor antagonists

TARITO once daily with food can be administered simultaneously with an H_2 -receptor antagonist or 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 should not exceed a dose comparable to famotidine 40 mg.

HMG-CoA reductase inhibitors

Atorvastatin Exposure may be increased during concomitant intake with TARITO. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including TARITO, are used in combination with atorvastatin. Caution should be exercised.

Immunosuppressants

Exposure to cyclosporin, tacrolimus, and sirolimus may be increased when they are co-administered with TARITO. Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with TARITO.

Inhaled/ nasal corticosteroids

TARITO is expected to increase fluticasone propionate exposures, resulting in a significant reduction in serum cortisol concentrations. Concomitant use of TARITO and fluticasone propionate is expected to produce systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. These effects could also occur with other corticosteroids metabolised via the cytochrome P450 3A pathway, e.g. budesonide. Concomitant use of TARITO with fluticasone propionate or other glucocorticoids that are metabolised by CYP3A4 is therefore not recommended.

Macrolide antibiotics

Exposure to clarithromycin is increased by co-administration with TARITO. Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a reduction in the dose of clarithromycin by 50 % should be considered when it is co-administered with TARITO.

Opioids

TARITO inhibits CYP3A4 and UGT1A1 therefore co-administration with buprenorphine increases concentrations of buprenorphine and norbuprenorphine. Clinical monitoring of sedation and cognitive effects is recommended. A dose reduction of buprenorphine may be considered.

Co-administration with methadone is expected to decrease methadone concentrations. A dosage increase in methadone may be considered.

Oral contraceptives

Alternate methods of non-hormonal contraception should be considered during treatment with TARITO. Administration of TARITO with ethinylestradiol and norgestimate decreases the mean concentration of ethinylestradiol by 20 % and increases the mean concentration of the active metabolite of norgestimate by 68 %. If an oral contraceptive is administered with TARITO, it is recommended that the oral contraceptive contain at least 30 µg of ethinylestradiol.

Co-administration of TARITO 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.

Fusidic acid

Co-administration of TARITO with fusidic acid is expected to significantly increase fusidic acid and ritonavir concentration in plasma.

Tobacco

Tobacco use is associated with an 18 % drop in the AUC of ritonavir which is an active constituent of TARITO.

The interaction of TARITO with the following medicines may result in serious adverse effects. Co-administration is therefore contraindicated.

Table 2: List of medicines whereby co-administration with PRODUCT NAME is contraindicated:

Contraindicated medicine within the class	**Clinical comments**
Alpha1-adrenoreceptor antagonist: Alfuzosin hydrochloride	Potential for hypotension caused by increased alfuzosin concentrations.
Analgesics: Pethidine, Piroxicam, Propoxyphene	Increased levels of these may result in increased risk of serious respiratory depression or haematologic abnormalities.
Antianginal: Ranolazine	Increased plasma concentrations of ranolazine may increase the potential of serious and/or life-threatening reactions**. (see section 4.5)**

Anticancer: Ventoclax	Increased plasma concentrations could result in increased risk of tumor lysis syndrome. **(see section 4.5)**
Antidysrhythmics: Amiodarone, bepridil, flecainide, propafenone, quinidine, encainide and digoxin	Potential for cardiac arrhythmias.
Antibiotics: Fusidic Acid	Increased plasma levels of fusidic acid and ritonavir which is an active constituent of TARITO.
Antifungal: Voriconazole	Significant decreases in voriconazole plasma concentrations may lead to loss of antifungal response.
Antigout: Colchicine	Potential for serious and/or life-threatening reactions in patients with renal or hepatic impairment.
Antihistamines: Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine, thereby, increasing the risk of serious dysrhythmias from these medicines.
Antimycobacterial: Rifampicin,	Rifampicin may decrease plasma concentrations of atazanavir which is an active substance of TARITO. This may result in reduced therapeutic effect and

	resistance.
Rifabutin	TARITO may increase concentrations of rifabutin leading to increased risk of adverse effects.
Antipsychotic/Neuroleptics:	
Blonanserin,	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin.
Lurasidone,	Increased concentrations of lurasidone may increase potential for serious and or life-threatening reactions.
Clozapine, Pimozide,	Increased concentrations of clozapine and pimozide may increase the risk of serious haematologic abnormalities.
Quetiapine	Increased concentrations of quetiapine may lead to coma.
Calcium Channel Blockers:	
Bipridil	Potential for serious and/or life-threatening adverse events.
Ergot derivatives:	
Dihydroergotamine, ergonovine, ergotamine and methylergonovine	Increased concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia of the extremities and other tissues.

Gastrointestinal motility medicine: Cisapride	Potential for cardiac dysrhythmias.
Herbal products: St John's Wort (*Hypericum perforatum*)	Co-administration may lead to a decrease in atazanavir and ritonavir levels, and to loss of virologic response and possible resistance to atazanavir and ritonavir or to the class of protease inhibitors.
HMG-CoA reductase inhibitors: Lovastatin and simvastatin	Increased concentrations of lovastatin and simvastatin therefore increasing potential for myopathy including rhabdomyolysis.
Long acting beta-adrenoreceptor agonist: Salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
Microsomal triglyceride transfer protein (MTTP) inhibitor: Lomitapide	May result in increased concentrations of lomitapide.
Neuroleptic: Pimozide	Potential for cardiac dysrhythmias.
PDE5 inhibitors: Sildenafil (when used for treatment of pulmonary arterial hypertension), **see section 4.4** and **section 4.5** for co-administration in patients with erectile dysfunction.	Increased potential for sildenafil associated adverse events (which include hypotension and syncope).

Avanafil, Vardenafil	Potential increase in concentrations of avanafil and vardenafil.
Protease inhibitors: Indinavir	Increased risk of hyperbilirubinemia when administered with TARITO.
Sedative/ hypnotics (Benzodiazepines): Midazolam, triazolam	Potential of increases in these highly metabolised sedatives and hypnotics resulting in the risk of prolonged or increased sedation or respiratory depression.
Antineoplastic: Irinotecan	Atazanavir which is an active of TARITO inhibits UGT and may interfere with the metabolism of irinotecan, resulting in toxicity.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The use of TARITO in pregnancy is contraindicated (see **section 5.2**).

The safety of TARITO in pregnancy has not been established.

Maternal adverse reactions:

Cases of lactic acidosis syndrome, sometimes fatal, have occurred in pregnant women using atazanavir in combination with nucleoside analogues, which are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take atazanavir, including pregnant women.

Advise pregnant women of the potential risks of lactic acidosis syndrome and hyperbilirubinemia.

Foetal/Neonatal adverse reactions:

All neonates exposed to atazanavir in utero should be monitored for severe hyperbilirubinemia during the first few days of life with a high risk of developing kernicterus with potentially irreversible brain damage.

Lactation

The use of TARITO is contraindicated in lactation, as safety has not been established. Both of the components of TARITO are secreted in human milk. Due to the risk of HIV transmission and the potential for adverse reactions in breast fed infants, women on treatment with TARITO should not breastfeed their infants.

Fertility

The effect on fertility has not been established.

Contraception:

Use of ritonavir, as in TARITO, may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative non-hormonal contraceptive method or an additional barrier method of contraception.

4.7 Effects on ability to drive and use machines

Adverse nervous system side effects, including somnolence and dizziness can occur with the use of TARITO and this could impact on the ability to drive and operate machinery.

4.8 Undesirable effects

Summary of side effect profile

The most common adverse events associated the combinations of atazanavir and ritonavir such as TARITO include nausea, diarrhoea, and jaundice. Jaundice is likely to occur within a few days to a few months after initiation of treatment.

Tabulated list of adverse reactions

The following adverse reactions have been classified in the following way: “Frequent, less frequent and frequency not known”.

Table 3: Adverse reactions associated with the fixed dosed combination of atazanavir and ritonavir:

System organ class	Side effects
Immune system disorders	**Frequent:** Allergic reactions including urticaria and face oedema. **Less frequent:** Anaphylaxis.
Metabolism and nutrition disorders	**Frequent:** Anorexia, weight loss.
Psychiatric disorders	**Frequent**: Anxiety, depression, insomnia.
Nervous system disorders	**Frequent:** Headache, somnolence, dizziness. **Less frequent:** Peripheral neuropathy, amnesia.
Cardiac disorders	**Less frequent:** Syncope, palpitation.
Vascular disorders	**Frequent**: Hypertension.
Respiratory, thoracic, and mediastinal disorders	**Less frequent:** Dyspnoea.
Gastrointestinal disorders	**Frequent**: Abdominal pain, diarrhoea, dyspepsia, nausea,

	vomiting, dry mouth, flatulence. **Less frequent:** Gastritis, pancreatitis.
Hepatobiliary disorders	**Frequent:** Hepatitis.
Skin and subcutaneous tissue disorders	**Frequent:** Rash, eczema, urticaria, vesiculobullous rash, pruritis. **Less frequent:** Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	**Frequent**: Myalgia, arthralgia arthrosis.
Renal and urinary disorders	**Frequent:** Haematuria, kidney pain.
General disorders and administration site conditions	**Frequent:** Asthenia, fever. **Less frequent:** Chest pain, malaise, abnormal gait.

Table 4: Adverse reactions associated with the individual active components of TARITO (atazanavir and ritonavir):

System organ class	Atazanavir-related side effects	Ritonavir-related side effects
Infections and infestations		**Frequent:** Pharyngitis.
Blood and lymphatic system disorders		**Frequent:** Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils. **Less frequent:** Anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis thrombocytopenia.

Endocrine system disorders		**Less frequent:** diabetes mellitus.
Metabolism and nutrition disorders	**Less frequent:** Increased appetite, weight gain.	**Frequent:** Hyperlipaemia, avitaminosis, cachexia, dehydration, glycosuria, gout, hypercholesteremia, peripheral oedema, oedema, redistribution/accumulation of body fat, hypertriglyceridemia. **Less frequent:** Diabetes mellitus, hyperglycaemia.
Psychiatric disorders	**Less frequent:** Sleep disorder, Abnormal dream, disorientation	**Frequent:** Agitation, confusion, emotional lability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking.
Nervous system disorders	**Frequent:** Dysgeusia.	**Frequent**: Circumoral paraesthesia, taste perversion, hyperesthesia, paraesthesia. **Less frequent:** Abnormal dreams, aphasia, ataxia, convulsion, incoordination, neuralgia, neuropathy, paralysis, parosmia, peripheral sensory neuropathy, taste loss, tremor, visual field defect. **Frequency not known:** Seizures
Eye disorders	**Frequent:** Scleral icterus.	**Frequent:** Abnormal vision,

		amblyopia/blurred vision, blepharitis, diplopia, eye pain, iritis, photophobia, uveitis.
Ear and labyrinth disorders		**Less frequent:** Ear pain, hearing impairment, increased cerumen, tinnitus, vertigo.
Cardiac disorders	**Less Frequent:** Torsades de pointes, oedema, QTc Prolongation **Frequency not known** (cannot be estimated from available data): Second degree AV block, third degree AV block.	**Less frequent:** Myocardial infarction.
Vascular disorders		**Frequent:** Haemorrhage, hypotension, migraine, peripheral vascular disorder, postural hypotension, tachycardia.
Respiratory, thoracic, and mediastinal disorders		**Frequent:** Increased cough, pharyngitis, oropharyngeal pain. **Less frequent:** Asthma, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder, rhinitis.
Gastrointestinal disorders	**Less frequent:** Stomatitis aphthous, abdominal distension.	**Frequent:** Eructation, local throat irritation, mouth ulcer, anorexia, gastrooesophageal reflux disease. **Less frequent:** Enlarged abdomen,

		abnormal stools, bloody diarrhoea cheilitis, colitis, constipation, dysphagia, oesophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal haemorrhage, gingivitis, ileitis, oral moniliasis, periodontal abscess, rectal disorder, tenesmus, thirst.
Hepatobiliary disorders	**Frequent:** Jaundice. **Less frequent:** Cholelithiasis, cholestasis, hepatosplenomegaly, cholecystitis.	**Frequent:** Cholangitis, hepatomegaly, liver damage, increased blood bilirubin.
Skin and subcutaneous tissue disorders	**Less frequent:** Alopecia, DRESS syndrome, angioedema, erythema multiforme, toxic skin eruptions, vasodilation.	**Frequent:** Maculopapular rash, sweating, acne, contact dermatitis, dry skin, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea. **Less frequent:** Toxic epidermal necrolysis (TEN).
Musculoskeletal and connective tissue disorders	**Less frequent:** Muscle atrophy, myopathy.	**Frequent:** Back pain, facial pain, joint disorder, muscle cramps, muscle weakness, myositis, neck pain, neck rigidity, twitching**.**
Renal and urinary	**Less frequent:** Pollakiuria,	**Frequent:** Dysuria, kidney calculus,

disorders	proteinuria, nephrolithiasis, interstitial nephritis, chronic kidney disease.	kidney failure, nocturia, polyuria, pyelonephritis, urethritis, urinary frequency, urinary retention.
Reproductive system and breast disorders	**Less frequent:** Gynaecomastia	**Frequent:** Menorrhagia **Less frequent:** Impotence, penis disorder.
General disorders and administration site conditions	**Frequent:** Fatigue.	**Frequent:** Flushing, feeling hot, pain, weight loss. **Less frequent:** Flu syndrome, chills, substernal chest pain.
Investigations		**Frequent:** Abnormal liver function tests, increased amylase, decreased free and total thyroxin. **Less frequent:** Abnormal electro-oculogram, abnormal electro-retinogram, altered hormone level, increased glucose, increased magnesium, increased alkaline phosphatase.
Injury and poisoning		**Less frequent:** Accidental injury, hypothermia.
Surgical and medical procedures:		**Frequent:** Vasodilation.

An inflammatory reaction to asymptomatic opportunistic infections may occur in HIV-infected patients with severe immune deficiency at the time of initiation of combination

antiretroviral therapy (cART). Autoimmune diseases such as Graves' disease may also occur many months after initiation of treatment.

Patients with advanced HIV disease and other risk factors may have osteonecrosis with. **(see section 4.4)**

Rashes are maculopapular skin eruptions that occur within the first 3 weeks of starting therapy.

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

Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Paediatric population

The most common adverse effects associated with the use of atazanavir which is contained in TARITO in paediatric patients include cough, fever, jaundice, rash, vomiting, diarrhoea, headache, peripheral oedema, extremity pain, nasal congestion, oropharyngeal pain, wheezing and rhinorrhoea.

Other special populations

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

Patients co-infected with hepatitis B and/or C that are being treated with TARITO are more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis.

Reporting of 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the

6.04 Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd (by e-mail: drugsafetysa@cipla.com or telephone: +2721 943 4200).

4.9 Overdose

In overdose, adverse events can be precipitated and/or be of increased severity.

Atazanavir

At high doses that lead to high medicine exposures, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations, may be observed.

Ritonavir

Paraesthesia has been reported. Renal failure with eosinophilia may present with ritonavir overdose.

Management of overdosage

Treatment of overdosage with TARITO should consist of general supportive measures, including monitoring of vital signs and electrocardiogram, and monitoring of patients' clinical status, serum unconjugated bilirubin levels and hepatic enzymes.

Administration of activated charcoal may be used to aid removal of unabsorbed medicine. There is no specific antidote for overdose with TARITO. Since TARITO is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of TARITO.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral Agents

Mechanism of action:

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

Ritonavir is a peptidomimectic inhibitor of HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease results in the inability of HIV-1 and HIV-2 aspartyl proteases to process the *gal-pol* polyprotein precursor and thereby resulting in production of HIV particles with immature morphology that cannot initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and minimally inhibits human aspartyl proteases.

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism.

Antiviral Activity in Cell Culture

Atazanavir exhibits anti-HIV-1 activity with a mean 50 % effective concentration (EC_{50}) in the absence of human serum of 2 to 5 nM against a variety of laboratory and clinical HIV-1 isolates grown in peripheral blood mononuclear cells, macrophages, CEM-SS cells, and MT-2 cells. ATV has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. ATV has variable activity against HIV-2 isolates (1,9-32 nM), with EC_{50} values above the EC_{50} values of failure isolates. Two-drug combination antiviral activity studies with ATV showed no antagonism in cell culture with PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), NNRTIs

(delavirdine, efavirenz, and nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir DF, and zidovudine), the HIV-1 fusion inhibitor enfuvirtide, and two compounds used in the treatment of viral hepatitis, adefovir and ribavirin, without enhanced cytotoxicity. The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of medicine that inhibits 50 % (EC_{50}) value of viral replication ranged from 3,8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC_{50} value for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 µM was required to inhibit cellular growth by 50 % resulting in a cell culture therapeutic index of at least 1000,2 Human immunodeficiency virus (HIV) protease inhibitors (PIs) are inhibitors of CYP3A enzymes, but the mechanism is poorly defined. Ernest CS et al.3 (2005) in his study, time- and concentration-dependent decreases in activity as defined by maximum rate of inactivation ($k_{(inact)}$) and inhibitor concentration that gives 50 % maximal inactivation (K(I)) of CYP3A by amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir were quantified using testosterone 6beta-hydroxylation as a marker for CYP3A activity with recombinant CYP3A4(+b(5)), recombinant CYP3A5, and pooled human liver microsomes (HLMs). All the PIs, except indinavir, displayed inactivation with CYP3A4(+b (5)) and HLMs. Ritonavir was the most potent (K(I) = 0,10 and 0,17 microM) and demonstrated high $k_{(inact)}$ values (0,32 and 0,40 min (-1)) with both CYP3A4(+b (5)) and HLMs. Ritonavir was not significantly depleted by high-affinity binding with CYP3A4(+b (5)) and confirmed that estimation of reversible inhibition was confounded with irreversible inhibition. For CYP3A5, nelfinavir exhibited the highest $k_{(inact)}$ (0.47 min (-1)), but ritonavir was the most potent (K(I) = 0,12 microM). Saquinavir and indinavir did not show time- and concentration-dependent decreases in

activity with CYP3A5. Spectrophotometrically determined metabolic intermediate complex formation was observed for all of the PIs with CYP3A4(+b (5)), except for lopinavir and saquinavir. The addition of nucleophilic and free aldehyde trapping medicines and free iron and reactive oxygen species scavengers did not prevent inactivation of CYP3A4(+b (5)) by ritonavir, amprenavir, or nelfinavir, but glutathione decreased the inactivation by saquinavir (17 %) and catalase decreased the inactivation by lopinavir (39 %). In conclusion, all the PIs exhibited mechanism-based inactivation, and predictions of the extent and time course of medicine interactions with PIs could be underestimated if based solely on reversible inhibition.

5.2 Pharmacokinetic properties

Atazanavir

There are no significant differences between atazanavir pharmacokinetics in healthy subjects compared to those of HIV-infected patients.

Pharmacokinetics if atazanavir exhibit a non-linear disposition.

Absorption

In HIV infected patients, multiple dosing of atazanavir 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV %) for atazanavir, C_{max} of 4466 (42 %) ng/mL, with time to C_{max} of approximately 2,5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76 %) ng/ml and 44185 (51 %) ng•h/mL, respectively.

Food effect: co-administration of atazanavir and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300 mg dose of atazanavir and 100 mg dose of ritonavir with a light meal result in a 33 % increase in the AUC and a 40 % increase in both the C_{max} and the 24-hour concentration of atazanavir relative to the

fasting state. Co-administration with a high-fat meal does not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11 % of fasting values. The 24-hour concentration following a high fat meal was increased by approximately 33 % due to delayed absorption; the median t_{max} increased from 2,0 to 5,0 hours. Administration of atazanavir with ritonavir with either a light or a high-fat meal decreases the coefficient of variation of AUC and C_{max} by approximately 25 % compared to the fasting state. To enhance bioavailability and minimise variability, TARITO is therefore to be taken with food.

Distribution

Atazanavir is approximately 86 % bound to human serum proteins over a concentration range of 100 to 10,000 ng/mL. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89 % and 86 %, respectively, at 1,000 ng/mL).

Biotransformation

Atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis.

Elimination

The mean elimination half-life of atazanavir is approximately 7 hours.

Special populations

Renal impairment:

In healthy subjects, the renal elimination of unchanged atazanavir is approximately 7 % of the administered dose. There are no pharmacokinetic data available for atazanavir with

ritonavir in patients with renal insufficiency. Atazanavir (without ritonavir) has been studied in adult patients with severe renal impairment. Results suggested that the atazanavir pharmacokinetic parameters were decreased by 30 % to 50 % in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown.

Hepatic impairment:

The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function. **(3DD2)**

Age/Gender:

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

Pregnancy:

Atazanavir peak concentrations and AUCs during the postpartum period (4-12 weeks) can be higher by approximately 26-40 % than in non-pregnant HIV infected patients. Plasma trough concentrations are expected to be 2-fold higher during the postpartum period when compared to thos in non-pregnant HIV infected patients.

Paediatric population:

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

Ritonavir

Absorption

The extent of absorption and absolute bioavailability of ritonavir have not been determined.

The extent of absorption of ritonavir 100 mg is increased by 12 % when administered with a high fat meal.

Distribution

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.

Ritonavir penetrates minimally into the brain.

Biotransformation

Ritonavir is extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform.

Five 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.

Elimination

Studies have shown that the elimination of ritonavir is primarily via the hepatobiliary system; approximately 86 % of radiolabel is 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.

Special populations

Gender/weight

There are no clinically significant differences in AUC or C_{max} between males and females. Ritonavir pharmacokinetic parameters are not statistically significantly associated with body weight or lean body mass.

Impaired renal function

Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

5.3 Preclinical safety data

No data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Anhydrous dibasic calcium phosphate
- Colloidal silicon dioxide
- Copovidone
- Crospovidone
- Hypromellose
- Iron oxide yellow
- Isopropyl alcohol
- Lactose monohydrate
- Magnesium stearate
- Methylene chloride

- Sodium stearyl fumarate,
- Sorbitan monolaurate
- Talc
- Opadry II 85G520033 yellow film-coating
- Purified water

Contents of the film-coating (Opadry):

- Iron oxide yellow
- Lecithin
- Macrogol
- Polyvinyl alcohol (partly hydrolysed)
- Talc
- Titanium dioxide.

6.2 Incompatibilities

NOT APPLICABLE

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

TARITO film-coated tablets are marketed in packs of 30's and packed into a white HDPE bottle that is fitted with a non-child resistant cap and contains 1 g silica gel bags and Rayon Sani coil.

TARITO film-coated tablets are marketed in Alu/Alu blisters containing 10 tablets per blister and ten (10) blisters are placed into an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

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Mobeni

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Customer Care: 080 222 6662

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8. REGISTRATION NUMBER

53/20.2.8/0093

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 JUNE 2020

10. DATE OF REVISION OF THE TEXT

20 February 2024