WARNING: CO-ADMINISTRATION OF ZATONAV WITH CERTAIN NON-SEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTIDYSRHYTHMICS OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF ZATONAV ON THE HEPATIC METABOLISM OF CERTAIN MEDICINES. SEE SECTIONS 4.3 AND 4.4.

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

ZATONAV film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZATONAV film-coated tablet contains 300 mg of atazanavir co-formulated with 100 mg of ritonavir as a pharmacokinetic enhancer.

Contains sugar: Each tablet contains lactose monohydrate 166,8 mg and sorbitol 100,0 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

A bilayer, film-coated, capsule shaped, biconvex tablet having one layer plain with pale yellow to yellow colour and a white to off-white layer debossed with “M777”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ZATONAV is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection.

4.2 Posology and method of administration

Adults: The recommended dose of ZATONAV is one tablet once daily taken with food. The ZATONAV tablets should be swallowed whole.

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal insufficiency:

No dosage adjustment is required.

Hepatic impairment:

ZATONAV has not been studied in patients with hepatic impairment.

ZATONAV should be used with caution in patients with mild hepatic impairment.

ZATONAV should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

Efavirenz: In treatment-naïve patients, it is recommended that ZATONAV be taken with efavirenz 600 mg (all once daily).

Tenofovir: When co-administered with tenofovir it is recommended that ZATONAV and tenofovir 300 mg, be taken all as a single daily dose with food.

4.3 Contraindications

- Known hypersensitivity to atazanavir, ritonavir, or any of the excipients of ZATONAV.
- Patients with hepatic impairment (see section 4.4).
- Concomitant administration with rifampicin.
- Concomitant administration with digoxin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, encainide, ergotamine, flecainide, pimozide, propafenone, quinidine, midazolam and triazolam.
- Safety and efficacy have not been established in the elderly.
- Pregnancy and lactation (see section 4.6).
- ZATONAV 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).

Medicines that are contraindicated with ZATONAV:

Medicine Class	**Clinical comment**
Alpha 1-adrenoreceptor antagonist: alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension.
Antidysrhythmics: quinidine	ZATONAV: Contraindicated due to potential for serious and/or life- threatening dysrhythmias.
Calcium Channel Blockers: bepridil	ZATONAV: Potential for serious and/or life-threatening adverse events.
Antimycobacterial: rifampicin	Rifampicin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect and development of resistance.
Calcium Channel Blockers: bepridil	ZATONAV: 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.
Proton pump inhibitors: omeprazole	Co-administration may reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
Herbal Products: St. John’s wort (*Hypericum perforatum*)	Patients taking ZATONAV should not use products/medicines 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 Other medicines, 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 ZATONAV has not been established for sildenafil when used for the treatment of pulmonary arterial hypertension. There is increased potential for sildenafil- associated adverse events.
Antineoplastic: irinotecan	ZATONAV inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Protease Inhibitor: indinavir	ZATONAV and indinavir are associated with hyperbilirubinaemia. Co-administration of ZATONAV and indinavir is not recommended (see section 4.8).

4.4 Special warnings and precautions for use

Based primarily on literature review, ritonavir is expected or has been shown to produce large increases in the plasma concentration of the following medicines: digoxin, amiodarone, bepridil, cisapride, dihydroergotamine, encainide, ergotamine, flecainide, pimozide, propafenone and quinidine. These medicines have recognised risks of dysrhythmias, haematologic abnormalities, seizures or other potentially serious adverse effects (see section 4.3).

Additionally, post-marketing reports of acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities have been associated with the co-administration of ritonavir and ergotamine or dihydroergotamine. These medicines should not be co-administered with ZATONAV (see section 4.3).

Ritonavir, in addition is likely to produce large increases in plasma concentrations of metabolized sedatives and hypnotics such as: midazolam and triazolam. Due to the potential for extreme sedation and respiratory depression from these medicines, they should not be co-administered with ZATONAV.

Atazanavir and ritonavir are principally metabolised by the liver. Ritonavir is eliminated by the liver. Therefore, caution should be exercised when administering ZATONAV to patients with hepatic impairment because atazanavir concentrations may be increased (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.

Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice have occurred in patients receiving atazanavir alone or in combination with other antiretroviral medicines. Therefore caution should be exercised when administering ZATONAV to patients with pre-existing mild to moderate liver disease, liver enzyme abnormalities or hepatitis. Increased AST/ALT monitoring should be considered in these patients especially at baseline during the first three months of ZATONAV treatment and as frequently as needed for the duration of treatment. There have been reports of hepatic dysfunction, including some fatalities, particularly in patients taking multiple concomitant medications and/or with advanced AIDS. ZATONAV is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Lipid disorders:

Treatment with ZATONAV therapy in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See section 4.5 on potential medicine interactions with ZATONAV and HMG-CoA Reductase Inhibitors (hypolipidaemics).

Laboratory tests and findings:

ZATONAV has been associated with alterations in triglycerides, ALT, AST, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating ZATONAV therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information

concerning laboratory test alterations associated with nucleoside analogues, medical practitioners should refer to the Professional information for each of these nucleoside medicines.

Adult patients: The most frequently reported laboratory abnormality in patients receiving regimens containing atazanavir and one or more NRTIs was elevated total bilirubin (87 % Grade 1, 2, 3 or 4). Grade 3 or 4 elevation of total bilirubin was noted in 36 % (20 % Grade 3, 6 % Grade 4, reported predominantly as elevated indirect bilirubin). Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2 % of patients receiving regimens containing atazanavir and one or more NRTIs included: elevated amylase (12 %), elevated creatine kinase (CK) (8 %), elevated ALT/SGPT (6 %), low neutrophils (6 %), elevated AST/SGOT (4 %) and elevated lipase (3 %).

The selection of antiretroviral therapy must be guided principally by antiviral efficacy. Consultation with standard guidelines for management of dyslipidaemia is recommended.

Pancreatitis:

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia and fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and ZATONAV therapy should be discontinued if a diagnosis of pancreatitis is made.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia. Also redistribution/accumulation of body fat which includes central obesity, dorso-cervical fat, enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, “Cushingoid appearance”, 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 inhibitors. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued treatment, hyperglycaemia persisted in some cases.

Immune Reconstitution Inflammatory Syndrome:

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). 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, *pneumocystis jirovecci* pneumonia, atypical mycobacterial infection, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune diseases (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 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.

PR Interval:

Atazanavir has the potential to prolong the PR interval of the electrocardiogram. ZATONAV should be used

with caution in patients with pre-existing conduction system disease. Caution should be used when co- administering ZATONAV with medicines known to induce PR interval prolongation.

Opportunistic infections:

Patients receiving ZATONAV 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.

Resistance/Cross-resistance:

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ZATONAV therapy 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 ZATONAV therapy will have on the activity of concordantly or subsequently administered protease inhibitors.

The risk of HIV transmission to others:

Patients must be advised that current antiretroviral therapy, including ZATONAV, does not prevent the risk of HIV transmission to others through sexual contact or blood contamination. Appropriate precautions must continue to be employed.

Rash:

Rashes are mostly mid-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with atazanavir, as contained in ZATONAV. ZATONAV should be discontinued if severe rash develops.

Dual PI Containing Combination Regimens:

Clinical experience with dual therapy including therapeutic doses of ritonavir with another protease inhibitor is limited. Ritonavir extensively inhibits the metabolism of most available protease inhibitors. Consideration of dual therapy with ritonavir should take into account the pharmacokinetic interaction and safety data of involved medicines. There is extensive cross-resistance in this class of medicines.

Lactose intolerance:

ZATONAV contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, (e.g. galactosaemia), the Lapp lactase deficiency, or glucose-galactose malabsorption should not take ZATONAV.

ZATONAV contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take ZATONAV.

4.5 Interaction with other medicines and other forms of interaction

Medicines which increase CYP3A activity (e.g. phenobarbital, carbamazepine, dexamethasone, phenytoin, rifampin and rifabutin) would be expected to increase the clearance of ZATONAV resulting in decreased ritonavir plasma concentrations.

ZATONAV has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP34A> CYP206> CYP2C9> CYP2C19>> CYP2A6, CYP1A2, CYP2E1. There is some evidence that ZATONAV may increase the activity of glucuronosyl glucuronyl transferase; thus, loss of therapeutic effects from directly glucuronidated medicines during ZATONAV therapy may signify the need for dosage alteration of these medicines. In addition to the medicines listed in the section 4.3, Table 1 summarises some commonly prescribed medicines, separated by the type of metabolism and expected magnitude of interaction when co-administered with ZATONAV. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir, and therefore ZATONAV. Dosage reductions may be required for those medicines extensively metabolized by CYP3A. Cardiac and neurologic events have been reported when ritonavir, as contained in ZATONAV, has been co-administered with disopyramide, mexiletine, nefazodone or fluoxetine. The possibility of medicine interaction cannot be excluded.

TABLE 1

Potential Effects on medicines co-administered with ritonavir as contained in ZATONAV

Medicine Category	**Representative Medicines by Potential Interaction Category**					
	Contraindicated Medicines	Large[1]	Moderate[1] ↑AUC2	Moderate[1]	Possible	Possible

		↑AUC2 (CYP3A)	(CYP2D6)	↑Or ↓AUC2 (CYP2C9/19)	↓AUC2 (Unknown CYP)	AUC2 (glucuronidation)
Analgesics, Narcotics		Alfentanil Fentanyl	Hydrocodone Oxycodone Propoxypene Tramadol		Levamethadyl (LAAM)	Codeine Hydromorphone Pethidine Methadone* Morphine
Analgesics, Non-steroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin Piroxicam	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Antidysrhythmic	Amiodarone Encainide Flecainide Propafenone Quinidine	Lidocaine	Disopyramide Mexiletine		Tocainide[11]	
Anti-asthmatic						Theophylline*
Antibiotic, Macrolide		Erythromycin	Clarithromycin*			
Antibiotic, Steroidal		Fusidic acid				
Anticonvulsa		Carbama	Clonazepam		Phenobarbito	Valproate

nt		zepine			ne	Ethosuximide
Antidepressant tricyclic			Amitriptyline Clomipramine Desipramine* Imipramine Maprotiline Nortriptyline Trimipramine		Doxepin[11]	
Antidepressant SSRIs and non-tricyclics		Nefazodone Sertraline	Bupropion Fluoxetine Paroxetine Trazodone* Venlafaxine		Fluvoxamine	
Antidiarrhoeal						Diphenoxylate Loperamide
Anti-emetics Prokinetics	Cisapride		Dronabinol Ondansetron		Prochlorperazine[11] Promethazine	Metoclopramide
Antifungal agents		Itraconazole Ketoconazole* Miconazole				

Antihistamines		Loratadine				
Antihypertensive				Losartan	Doxazosin[11] Prazosin[11] Terazosin[11]	
Antimycobacterial		Rifabutin*			Ethionamide Rifampin	
Antiparasitics		Quinine		Proguanil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine Trimetrexate	Atovaquone
Antiulcer agents				Lansoprazole Omeprazole		
Beta-blockers Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nimodipine	Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betazolol[1]	

		Nisoldipine Nitrendipine Verapamil				
Cancer chemo-therapeutic		Tamoxifen	Etoposide Paclitaxel Vinblastine Vincristine	Cyclophosphamide[3] Ifosfamide		Daunorubicin[11] Doxorubicin[11]
Ergot alkaloids and derivatives	Dihydroergotamine	Bromocriptine			Ergonovine[11] Methylergonovine[11] Methysergide1	
Haemorheologic agent					Pentoxifylline	
HIV antivirals		Indinavir* Saquinavir*			Nevirapine[11]	
Hypoglycaemics				Glimepiride Glipizide Glyburide Tolbutamide		
Hypolipidaemics		Atorvastatin Lovastatin Simvastat			Gemfibrozil	Clofibrate

		in				
Immunosuppressants		Ciclosporin Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide			Chlorpromazine Haloperidol Perphenazine Risperidone Thioridazine		Clozapine
Sedatives/hypnotics	Midazolam Triazolam	Buspirone		Clorazepate Diazepam Estazolam Flurazepam Zolpidem		Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*		Prednisone		Ethinyl estradiol*
Stimulants				Dexfenfluramine Methampheta mine	Methylphenidate	

[1] Large = > 3X; Moderate = 1.5-3X

[2] AUC = area under the plasma concentration-time curve, a measure of substance exposure.

[3] An increase in the AUC of cyclophosphamide and ifosfamide, both activated by CYP, may correspond to a decrease in the AUC of the active metabolite(s) and a possible decrease in efficacy of these medicines.

[11] A possible increase in concentration is more likely when combined with ritonavir.

* Clinical medicine interaction study has been performed.

Alprazolam:

Co-administration of alprazolam with ritonavir resulted in statistically significant decrease in mean alprazolam C_{max} values (16 %) but not in mean AUC values (12 %). Similarly, a statistically significant effect was observed on the sedation effect curve but not on the extent of sedation. Mild psychomotor impairment was confounded by a learning effect. These pharmacokinetic and pharmacodynamic results are inconsistent when considering the pharmacologic effect of alprazolam.

Amprenavir:

Concentrations of the HIV-protease inhibitor, amprenavir are increased when co- administered with ritonavir.

Buspirone:

Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone with substances that potentially inhibit CYP3A, such as ritonavir is expected to substantially elevate buspirone levels. When co-administered with ritonavir, a dose reduction or low dose of buspirone used cautiously is recommended.

Clarithromycin:

Concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31 %, C_{min} increased by 182 % and AUC increased by 77 % with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment the following dosage adjustments should be considered. For patients with CrCl 30 to 60 ml/min the dose of clarithromycin should be reduced by 50

%. For patients with CrCl 30 ml/min the dose of clarithromycin should be decreased by 75 %. Doses of clarithromycin greater than 1 gram per day should not be co-administered with ritonavir.

Caution is advised in patients with cardiac disorders as clarithromycin use is associated with QT prolongation, torsades de pointes and cardiac arrest.

Delavirdine:

Delavirdine is an inhibitor of CYP3A-mediated metabolism. In a published study, concurrent administration of clinical doses of delavirdine 400 mg three times daily with ritonavir 600 mg twice daily (n=12 HIV-infected patients) was reported to increase steady-state ritonavir C_{max} AUC by approximately 50 % and C_{min} by about 75 %.

Desipramine:

Co-administration of ritonavir with desipramine resulted in a 145 % mean increase in the AUC of desipramine. Dosage reduction of desipramine should be considered in patients taking the combination.

Digoxin:

Co-administration of ritonavir as contained in ZATONAV and digoxin will result in significantly increased digoxin levels and related side effects. Digoxin is contraindicated in patients taking ZATONAV.

Inhaled/nasal corticosteroid:

Concomitant use of ZATONAV 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, as contained in ZATONAV, 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, concomitantuse of ZATONAV and fluticasone propionate or other glucocorticoids that are metabolised by CYP3A4 is not recommended.

Fusidic acid:

Co-administration of ritonavir with fusidic acid is expected to significantly increase fusidic acid and ritonavir concentrations in plasma. ZATONAV should not be co-administered with fusidic acid.

***Hypericum perforatum* (St. John's Wort):**

Patients on ZATONAV should not use concomitantly medicines containing St. John's Wort *(Hypericum perforatum)* since it may be expected to result in reduced plasma concentrations of ritonavir. This effect may be due to induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance.

Indinavir:

Ritonavir inhibits the CYP3A-mediated metabolism of indinavir. In healthy subjects, 200 to 400 mg of ritonavir twice daily given with a single 400 mg to 600 mg indinavir dose increased the indinavir AUC by 185 to 475 %, C_{max} 21 % to 110 % and C_{min} 11 to 33-fold, relative to 400 and 600 mg indinavir given alone. Concomitant administration of 400 mg ritonavir and 400 mg of indinavir twice daily with a meal yielded a similar indinavir AUC, a 4-fold increase in C_{min} and a 50 % to 60 % decrease in C_{max} as compared to those resulting from administration of indinavir 800 mg three times daily under fasting conditions. Coadministration of ritonavir with indinavir will result in increased indinavir serum concentrations. There are limited safety data or efficacy data available on the use of this combination in patients.

The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole:

Concomitant administration of ritonavir (500 mg every 12 hours) and ketoconazole (200 mg four times daily) resulted in an increase of mean ketoconazoleAUC24 and C_{max} by 244 % and 55 %, respectively. The mean half-life of ketoconazole increased from 2,7 to 13,2 h. Mean AUC_{24} and C_{max} of ritonavir increased by 18 and 10 % respectively. No dosage adjustment of ritonavir is necessary; however doses of ketoconazole 200 mg/day or greater should be used with caution in combination with ritonavir and a decreased dosage may be considered.

Methadone:

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

Nelfinavir:

Interactions between ZATONAV and nelfinavir are likely to involve both cytochrome P450 inhibition

and induction. Concurrent ritonavir 400 mg twice daily significantly increases the concentrations of M8 (the major active metabolite of nelfinavir) and results in a smaller increase in nelfinavir concentrations. In a study in ten patients, nelfinavir 750 mg and ritonavir 400 mg twice daily yielded slightly higher nelfinavir AUC (160 %), C_{max} (121 %) and C_{trough} (123 %) than historical data for nelfinavir 750 mg three times daily monotherapy. The AUC of M8 was increased by 347 %.

Oral Contraceptive or Patch Contraceptive:

A pharmacokinetic study demonstrated that the concomitant administration of ZATONAV 500 mg every 12 hours and a fixed-combination oral contraceptive resulted in reductions of the ethinyl oestradiol mean C_{max} and mean AUC by 32 % and 40 %, respectively. Increased doses of oral contraceptives or patch contraceptives containing ethinyl oestradiol, or alternate methods of contraception, should be considered.

Rifabutin:

Concomitant administration of ZATONAV 500 mg every 12 hours and rifabutin resulted in an approximate 4-fold and 35-fold increase in the AUC of rifabutin and its active metabolite 25-O-deacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials. Dosage reduction of rifabutin by at least three- quarters of the usual dose of 300 mg/day is recommended (e.g. 150 mg every other day or three times a week). Further dosage reduction may be necessary.

Saquinavir:

Ritonavir extensively inhibits the metabolism of saquinavir which will greatly increase saquinavir plasma concentrations. Following approximately four weeks of a combination regimen of saquinavir (400 or 600 mg twice daily) and ritonavir (400 or 600 mg twice daily) in HIV-infected patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 500 mg three times daily without ritonavir. When used in combination therapy for up to 24 weeks, doses greater than 400 mg twice daily of either ritonavir or saquinavir were associated with an increase in adverse events.

Sildenafil:

PDE5-inhibitors (including Sildenafil) are contraindicated for concomitant use with ZATONAV. Co-administration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including

hypotension, syncope, visual changes and prolonged erection.

Sulfamethoxazole/trimethoprim:

Concomitant administration of ritonavir 500 mg every 12 hours and sulfamethoxazole/ trimethoprim resulted in a 20 % reduction of the sulfamethoxazole AUC and a 20 % increase of the trimethoprim AUC.

Tadalafil:

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events.

Theophylline:

Concomitant administration of ritonavir 500 mg every 12 hours and theophylline resulted in a 43 % decrease in the AUC of theophylline. An increased dosage of theophylline may be required.

Tobacco:

Tobacco use is associated with an 18 % decrease in the AUC or ritonavir.

Trazodone:

Concomitant use of ZATONAV and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Vardenafil:

Use vardenafil with caution at reduced doses of no more than 2,5 mg every 72 hours with increased monitoring for adverse events.

Voriconazole:

Co-administration of ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82 %; therefore, co-administration of these substances is contraindicated.

Zidovudine:

Concomitant administration of ritonavir 300 mg every 6 hours and zidovudine (AZT) 200 mg every 8 hours resulted in a reduction of the zidovudine C_{max} and AUC of 27 % and 25 %, respectively. Ritonavir pharmacokinetics were not significantly affected. Dose alteration of AZT during concomitant ritonavir

therapy should not be necessary.

Interactions and effects on AUC and Cmax of co-administration with ritonavir as shown in Table 2 below:

TABLE 2

Effect on ritonavir AUC and Cmax with **Co-administration of ritonavir with other medicines**

Medicine	**Ritonavir dosage**	**n**	**AUC % (95 CI)**	**C_{max} % (95 CI)**
Clarithromycin 500 mg 12 hourly 4 days	200 mg 8 hourly 4 days	22	↑12 % (2,23 %)	↑15 % (2,28 %)
Didanosine 200 mg 12 hourly 4 days	600 mg 12 hourly 4 days	12	↔	↔
Fluconazole 400 mg day 1 200 mg daily 4 days	200 mg 5 hourly 4 days	8	↑12 % (5, 20 %)	↑15 % (7,22 %)
Fluoxetine 30 mg 12 hourly 8 days	600 mg single dose	16	↑19 % (7,34 %)	
Rifampicin 600 mg or 300 mg daily 10 days[1]	500 mg 12 hourly 20 days	7,9*	↓-35 % (7,55 %)	↓-25 % (-5,46 %)
Zidovudine 200 mg 8 hourly 4 days	300 mg 6 hourly 4 days	10	↔	↔

[1] Preliminary data

↑ Indicates increase

↓ Indicates decrease

↔ Indicates no change

* Parallel group design; entries are subjects receiving combination and control regimens, respectively.

Atazanavir is metabolised in the liver by the cytochrome P450 enzyme system and is an inhibitor of CYP3A4 (cytochrome P450 3A4). Co-administration of atazanavir 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 substance that could increase or prolong both its therapeutic and adverse effects. Co-administration of atazanavir as contained in ZATONAV and medicines that induce CYP3A4, such as rifampicin, may decrease atazanavir plasma concentrations and reduce its therapeutic effect. Co-administration of atazanavir as contained in ZATONAV and substances that inhibit CYP3A4 may increase atazanavir plasma concentrations. The magnitude of CYP3A4-mediated medicine interactions (effect on atazanavir as contained in ZATONAV or effect on co-administered medicines) may change when atazanavir as contained in ZATONAV is co-administered with ritonavir, a potent CYP3A4 inhibitor.

Caution should be used when co-administering atazanavir as contained in ZATONAV with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, verapamil) (see section 4.4).

Medicines that should not be administered with atazanavir as contained in ZATONAV:

Antidysrhythmics (amiodarone, systemic lidocaine and quinidine):

Contraindicated if atazanavir as in ZATONAV is co-administered with ritonavir as in ZATONAV due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

The co-administration of antidysrhythmics (amiodarone, systemic lidocaine and quinidine) with ZATONAV has the potential to produce serious and/or life-threatening adverse events as a result of increased concentrations of the antidysrhythmics.

Antimycobacterial:

Rifampicin: Rifampicin substantially decreases plasma concentrations of atazanavir as contained in ZATONAV, which may result in loss of therapeutic effect and development of resistance.

Rifabutin: A rifabutin dose reduction of up to 75 % (e.g. 150 mg every other day or 3 times per week) is recommended as co-administration with ZATONAV may increase rifabutin plasma concentrations.

Antineoplastic: Irinotecan: Atazanavir as contained in ZATONAV inhibits UGT (Uridine 5 diphospho glucuronosyl transferase) and may interfere with the metabolism of irinotecan, resulting in increased

irinotecan toxicities.

Calcium channel blockers: Bepridil: Potential for serious and/or life-threatening adverse events (see section 4.3).

Diltiazem:

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

Felodipine, nifedipine, nicardipine, and verapamil: Caution is warranted. Dose titration of the calcium channel blocker should be considered and ECG monitoring is recommended.

Ergot derivatives: Dihydroergotamine, ergotamine, ergonovine, methylergonovine: Contraindicated due to 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: Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

HMG Co-A reductase inhibitor: Lovastatin, simvastatin: There is a potential for serious reactions such as myopathy including rhabdomyolysis.

Atorvastatin: Exposure to atorvastatin may be increased when it is co-administered with ZATONAV. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including ZATONAV, are used in combination with atorvastatin. Concomitant administration is contraindicated.

Neuroleptic: Pimozide: Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Protease inhibitor: Indinavir: Atazanavir as contained in ZATONAV is associated with hyperbilirubinaemia. Co-administration of ZATONAV and indinavir is contraindicated.

Saquinavir: Co-administration may lead to an increased saquinavir concentration. Appropriate dosing recommendations with respect to efficacy and safety for this combination, with or without ritonavir, have not been established. Although not studied, the co-administration of ZATONAV with other protease inhibitors would be expected to increase exposure to the other protease inhibitors and is not recommended.

Proton pump inhibitors: Atazanavir, as contained in ZATONAV, should not be administered with proton pump inhibitors due to a substantial decrease in atazanavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Sedative hypnotics: Midazolam, triazolam: Contraindicated due to potential for increased concentrations of the sedative hypnotic and increased risk of prolonged sedation or respiratory depression.

Herbal medicines: St. John'sWort (*Hypericum perforatum*):

Patients taking atazanavir as contained in ZATONAV should not use products containing St. John's Wort *(Hypericum perforatum)* because co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.

Nucleoside reverse transcriptase inhibitors (NRTIs): Didanosine: Co-administration of didanosine buffered tablets and atazanavir as contained in ZATONAV markedly decreased exposure to atazanavir (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets. Co-administration of the enteric-coated formulation of didanosine with atazanavir or atazanavir/ritonavir and a light meal decreased exposure to didanosine (see section 4.2: Concomitant therapy).

Tenofovir: Exposure to atazanavir is decreased when tenofovir is co-administered with atazanavir as contained in ZATONAV (see section 4.2: Concomitant therapy). Atazanavir as contained in ZATONAV increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir- associated adverse events, including renal disorders. Patients receiving ZATONAV and tenofovir should be monitored for tenofovir-associated adverse events.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz: Exposure to atazanavir is decreased when efavirenz is co-administered with ZATONAV (see section 4.2).

Nevirapine: Nevirapine, an inducer of CYP3A4, is expected to decrease ZATONAV exposure. In the absence of data, co-administration of ZATONAV and ritonavir is not recommended.

Other:

Antacids and buffered medicines: Reduced plasma concentrations of atazanavir as contained in ZATONAV may result if antacids, including buffered medications, are administered with atazanavir.

ZATONAV should be administered 2 hours before or 1 hour after these medications.

Anticoagulants:

Warfarin: The co-administration of warfarin with ZATONAV may potentially produce serious and/or life-threatening bleeding as a result of an increase in the warfarin plasma concentration. It is recommended that international normalized ratio (INR) be frequently monitored.

Antidepressants:

Tricyclic antidepressants: The co-administration of tricyclic antidepressants with ZATONAV may potentially produce serious and/or life-threatening adverse events as a result of an increase in the tricyclic antidepressants concentration.

Trazodone: Concomitant use of trazodone and ZATONAV with or without ritonavir may increase plasma concentrations of trazodone, thereby resulting in increased trazodone adverse events e.g. nausea, dizziness, hypotension and syncope. If trazodone is used with a CYP3A4 inhibitor such as atazanavir, as contained in ZATONAV, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals:

Ketoconazole and itraconazole: High doses of ketoconazole and itraconazole (> 200 mg/day) should be used with caution with ZATONAV.

Voriconazole: Should not be administered to patients receiving ZATONAV.

Erectile dysfunction agents:

Phosphodiesterase (PDE5) inhibitors (e.g. sildenafil, tadalafil, or vardenafil): Co-administration of ZATONAV with a PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentrations and potentially result in an increase in PDE5 inhibitor-associated adverse events.

H2-receptor antagonists: Plasma concentrations of atazanavir were substantially decreased when atazanavir 400 mg once daily was administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance.

Immunosuppressants:

Ciclosporin, sirolimus, tacrolimus:

Exposure to ciclosporin, tacrolimus and sirolimus may be increased when they are co-administered with ZATONAV.

Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ZATONAV.

Macrolide antibiotics:

Clarithromycin: Exposure to clarithromycin is increased when coadministration with ZATONAV. As increased concentrations of clarithromycin may cause QTc prolongations, a 50 % dose reduction of clarithromycin should be considered when co-administered with ZATONAV.

Oral contraceptives:

Ethinyl estradiol and norethindrone: Mean concentrations of ethinyl estradiol and norethindrone are increased when they are co-administered with atazanavir, and therefore ZATONAV.

Decreased HDL or increased insulin resistance may be associated with increased concentrations of norethindrone, particularly in diabetic women. The use of oral contraceptives is contraindicated. Alternate methods of non-hormonal contraception should be used.

4.6 Fertility, pregnancy and lactation

ZATONAV is contraindicated in pregnancy and lactation, as safety has not been established.

Women on treatment with ZATONAV should not breastfeed their infants. Transfer of one or both active ingredients into breastmilk in concentrations that may harm the baby cannot be excluded.

It is recommended that HIV infected women do not breastfeed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

ZATONAV may influence the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with ZATONAV affects them. Dizziness, somnolence, disorientation, blurred vision and syncope have been reported in patients on treatment with ZATONAV.

4.8 Undesirable effects

Side effects have been reported.

Atazanavir:

Immune system disorders:

Less frequent: Allergic reaction.

Metabolism and nutrition disorders:

Less frequent: Decreased weight, weight gain, anorexia, increased appetite.

Psychiatric disorders:

Less frequent: Depression, disorientation, anxiety, insomnia, sleep disorder, confusion, abnormal dreams.

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Peripheral neuropathy, syncope, amnesia, somnolence, abnormal gait, dysgeusia.

Eye disorders:

Frequent: Ocular icterus.

Cardiac disorders:

Less frequent: Oedema, palpitation, torsade de pointes*,* QTc prolongation.

Vascular disorders:

Less frequent: Hypertension, syncope.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea.

Gastrointestinal disorders:

*Frequent: V*omiting, diarrhoea, abdominal pain, nausea, dyspepsia.

*Less frequent: P*ancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth.

Hepatobiliary disorders:

Frequent: Jaundice.

Less frequent: Hepatitis, hepatosplenomegaly, cholelithiasis*,* cholestasis*,* cholecystitis.

Skin and subcutaneous tissue disorders:

Frequent: Rash

Less frequent: Urticaria, alopecia, pruritus, vesiculobullous rash, eczema, vasodilatation, medicine rash with eosinophilia and systemic symptoms (DRESS) syndrome*,* eruptions*,* Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Less frequent: Muscle atrophy, arthralgia, myalgia, myopathy.

Renal and urinary disorders:

Less frequent: Nephrolithiasis, haematuria, proteinuria, pollakiuria, kidney pain.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia.

General disorders and administration site conditions:

Frequent: Lipodystrophy syndrome, fatigue.

Less frequent: Chest pain, fever, malaise, pyrexia, asthenia, gait disturbance.

Ritonavir:

Infections and infestations:

Frequent: Pharyngitis.

Blood and the lymphatic system disorders:

Frequent: Decreased white blood count, decreased haemoglobin, decreased neutrophils, increased eosinophils.

Less frequent: Increased white blood count, increased neutrophils and increased prothrombin time, anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis.

Frequency unknown: Thrombocytopenia.

Immune system disorders:

Frequent: Allergic reactions including urticaria, face oedema.

Less frequent: Anaphylaxis and Stevens-Johnson syndrome.

Metabolism and nutrition disorders:

Frequent: Anorexia, hyperlipidaemia, weight loss.

Less frequent: Dehydration, diabetes mellitus, hyperglycaemia, avitaminosis, cachexia, oedema,

glycosuria, gout, hypercholesterolaemia, peripheral oedema, redistribution/accumulation of body fat (see section 4.4).

*Frequency u*nknown: Hypertriglyceridaemia, hyperuricaemia.

Psychiatric disorders:

Frequent: Anxiety.

Less frequently: Agitation, confusion, depression, emotional liability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking.

Nervous system disorders:

Frequent: Dizziness, paraesthesia, hyperaesthesia, somnolence, circumoral paraesthesia, headache, taste perversion.

Frequency unknown: Seizure, syncope, abnormal dreams, amnesia, aphasia, ataxia, convulsion, grand mal convulsion, incoordination, neuralgia, neuropathy, paralysis, parosmia, peripheral neuropathy, peripheral sensory neuropathy, taste loss, tremor, visual field defect.

Eye disorders:

Less 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: Palpitations, syncope.

Frequency unknown: Tachycardia, myocardial infarction.

Vascular disorders:

Frequent: Vasodilation.

Less frequent: Haemorrhage, hypotension including orthostatic hypotension, migraine, peripheral vascular disorder, postural hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Pharyngitis, increased cough.

Less frequent: Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder and rhinitis.

Gastrointestinal disorders:

Frequent: Abdominal pain, nausea, diarrhoea, vomiting, dyspepsia, anorexia, local throat irritation, flatulence, dry mouth, eructation, mouth ulcer.

Less frequent: Enlarged abdomen, abnormal stools, bloody diarrhoea, cheilitis, colitis, constipation, dysphagia, oesophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal haemorrhage, gingivitis, ileitis, oral moniliasis, pancreatitis, periodontal abscess, rectal disorder, tenesmus, thirst.

Hepatobiliary disorders:

Less frequent: Hepatitis, jaundice, cholangitis, hepatomegaly, liver damage.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, sweating, lipodystrophy, maculopapular rash.

Less frequent: Acne, contact dermatitis, dry skin, eczema, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea, urticaria, vesiculobullous rash.

Musculoskeletal and connective tissue disorders:

Frequent: Myalgia.

Less frequent: Myositis, rhabdomyolysis, arthralgia, arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness, neck pain, neck rigidity, twitching.

Renal and urinary disorders:

Less frequent: Dysuria, haematuria, kidney calculus, kidney failure, kidney pain, nocturia, polyuria, pyelonephritis, urethritis, urinary frequency, urinary retention.

Frequency unknown: Acute renal failure.

Reproductive system and breast disorders:

Less frequent: Impotence, penis disorder.

Frequency unknown: Menorrhagia.

General disorders and administration site conditions:

Frequent: Asthenia, fever, pain, weight loss.

Less frequent: Abnormal gait, chest pain, chills, flu syndrome, malaise, substernal chest pain.

Investigations:

Frequent: Abnormal liver function tests.

Less frequent: Abnormal electro-oculogram, abnormal electroretinogram, altered hormone level.

Injury and poisoning:

Less frequent: Accidental injury, hypothermia.

Surgical and medical procedures

Frequent: Vasodilation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZATONAV is important. It allows continued monitoring of the benefit/risk balance of the medicine.mHealth care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose with ZATONAV side effects of both Atazanavir and Ritonavir can be precipitated and/or be of increased severity.

Atazanavir:

Human experience of acute overdose with atazanavir is limited. In overdose, side effects of atazanavir can be precipitated and/or be of increased in severity. Jaundice due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations may be observed.

Ritonavir:

Human experience of acute overdose with ritonavir is limited. In overdose, side effects of ritonavir can be precipitated and/or be of increased severity. Paraesthesias and renal failure with eosinophilia have been reported with ZATONAV overdose.

Management of overdosage:

There is no specific antidote for overdose with ZATONAV. Treatment of overdose with ZATONAV should consist of general supportive and symptomatic treatment measures including monitoring of vital signs and observation of the clinical status of the patient. Since ZATONAV is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease

inhibitors ATC code: J05AR26

Atazanavir:

Atazanavir is an azapeptide HIV-1 protease inhibitor (PI).

The compound selectively inhibits the virus-specific processing of viral *Gag-Pol* proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Resistance *in vitro:*

ATAZANAVIR resistant viruses were detected in patients on atazanavir-containing regimens depending on whether patients had previously received protease inhibitor therapy and whether their study treatment utilized atazanavir as the only protease inhibitor or atazanavir plus saquinavir. Of the 23 resistant isolates emerging in treatment-naïve patient studies, all had a 150L substitution emerge on atazanavir therapy. Phenotypic analysis of the 150L-containing isolates showed atazanavir-specific resistance, which coincided with increased susceptibility to other protease inhibitors.

The 150L substitution, sometimes in combination with an A71V change, is the signature resistance change for atazanavir. There was no evidence of cross-resistance between atazanavir and amprenavir.

Cross-resistance *in vitro* to viruses resistant to other protease inhibitors:

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.

Ritonavir:

Ritonavir is a pharmacokinetic enhancer:

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

5.2 Pharmacokinetic properties

Atazanavir:

Pharmacokinetic properties:

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

Multiple dosing of atazanavir sulphate 400 mg once daily with a light meal produced peak steady state atazanavir plasma concentrations approximately 2,7 hours after administration. Steady-state for atazanavir was achieved between day 4 and 8.

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

Atazanavir is 86 % bound to human serum-proteins.

Atazanavir is principally metabolised by the CYP3A 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.

Ritonavir:

Absorption:

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability

have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV-infected adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. The time to maximum concentration (T_{max}) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0,1 L/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosing schemes of ritonavir alone are shown in the table below. Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatine capsule under fed conditions.

Ritonavir dosing regimen		
	100 mg once daily	**100 mg twice daily[1]**
C_{max} (µg/ml)	0,84 ± 0,39	0,89
C_{trough} (µg/ml)	0,08 ± 0,04	0,22
AUC 12 or 24 (µg.h/ml)	6,6 ± 2,4	6,2
t ½ (h)	~ 5	~ 5
Cl/F (L/h)	17,2 ± 6,6	16,1

[1] Values expressed as geometric means. Note: ritonavir was dosed after a meal for all listed regimens.

Effects of food on oral absorption:

Food slightly decreases the bioavailability of the ritonavir in the tablet.

Administration of a single 100 mg dose of ritonavir in a tablet with a moderate fat meal (857 kcal, 31 % calories from fat) or a high fat meal (907 kcal, 52 % calories from fat) was associated with a mean decrease of 20 – 23 % in ritonavir AUC and C_{max}.

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.

Metabolism:

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

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

Elimination:

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86 % of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

Patients with impaired liver function:

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

Patients with 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

Atazanavir:

In repeat-dose toxicity studies conducted in mice, rats, and dogs, atazanavir-related findings were generally confined to the liver and included generally minimal to mild increases in serum bilirubin and

liver enzymes, hepatocellular vacuolation and hypertrophy, and, in female mice only, hepatic single-cell necrosis.

During *in vitro* studies, cloned human cardiac potassium channel (hERG), was inhibited by 15 % at a concentration (30 µM) of atazanavir corresponding to 30- fold the free drug concentration at C_{max} in humans. Similar concentrations of atazanavir increased by 13 % the action potential duration (APD90) in the rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes.

The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

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

Atazanavir was negative in an Ames reverse-mutation assay but did induce chromosomal aberrations *in vitro* in both the absence and presence of metabolic activation. In long-term carcinogenicity studies of atazanavir in mice and rats, an increased incidence of benign hepatic adenomas was seen in female mice only.

This is considered likely secondary to cytotoxic liver changes manifested by single-cell necrosis and is considered to have no relevance for humans at intended therapeutic exposures. There were no tumorigenic findings in male mice or in rats.

Ritonavir:

Ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including

the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, copovidone, crospovidone, magnesium stearate, maize starch, microcrystalline cellulose, sodium chloride, sodium stearyl fumarate, sorbitan monolaurate, sorbitol, film-coat (hypromellose, macrogol).

Lactose monohydrate (sugar) 166,8 mg.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle pack (marketable pack) comprises of white coloured HDPE bottle with white opaque polypropylene (PP) screw cap.

High density polyethylene (HDPE) bottle pack (marketable pack) comprises of white coloured HDPE bottle (pill jar) with white opaque polypropylene (PP) tamper evident closure with inbuilt plastic canister silica gel

desiccant.

Pack size of 30’s.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando, Gauteng

1609

8 REGISTRATION NUMBER

45/20.28/0925

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2020

10 DATE OF REVISION OF THE TEXT

15 March 2023