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WARNING: CO-ADMINISTRATION OF ZANRIT 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 ZANRIT ON THE HEPATIC METABOLISM OF CERTAIN MEDICINES. SEE SECTIONS 4.3 AND 4.5.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZANRIT 300/100 mg**,** film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Atazanavir sulphate equivalent to 300 mg atazanavir and ritonavir 100 mg.

Each tablet contains sugar (lactose monohydrate 167,292 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

ZANRIT is a bilayer, capsule shaped, biconvex, film coated tablet, having one layer with white to pale yellow colour and other white to off-white colour, plain on both the sides. A thin line on the tablet side may be visible.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The recommended dose for adults is:

One tablet, once a day taken orally, with food. The tablet should be swallowed whole.

Special populations

Concomitant therapy

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

Tenofovir: When co-administered with tenofovir, it is recommended that ZANRIT be given with tenofovir 300 mg, all as a single daily dose with food (see section 4.5).

Renal impairment

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

Hepatic impairment

Atazanavir in combination with ritonavir, as contained in ZANRIT, has not been studied in subjects with hepatic impairment. ZANRIT should be used with caution in patients with mild hepatic impairment. ZANRIT should not be used in patients with moderate and severe hepatic impairment (see section 4.3).

Elderly

No data are available on which to make a dose recommendation for patients above 65 years.

Method of administration

ZANRIT is to be taken orally, with food.

Missed dose

Doctors should advise patients who forget to take ZANRIT to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- hypersensitivity to atazanavir, ritonavir or to any of the ingredients of ZANRIT listed in section 6.1
- concomitant administration with digoxin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, encainide, ergotamine, flecainide, pimozide,

propafenone, quinidine, midazolam and triazolam (see section 4.5)

- moderate to severe liver disease (see section 4.4)
- pregnancy and lactation
- co-administration 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 table 1 below and section 4.5).

Table 1 – Medicines that are contraindicated with ZANRIT

Medicine Class	**Medicines Contraindicated**	**Clinical Comment**
Alpha1-adrenoreceptor antagonist	Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension.
Anti-dysrhythmics	Quinidine	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Antifungal	Voriconazole	Voriconazole should not be administered to patients receiving ZANRIT.
Antimycobacterial	Rifampicin	Rifampicin substantially decreases plasma concentrations of atazanavir,

		which may result in loss of therapeutic effect and development of resistance.
Antipsychotics/ Neuroleptics	Bionanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with bionanserin.
	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Calcium Channel Blockers:	Bepridil	Potential for serious and/or life-threatening adverse events.
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
GI Motility Medicine	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Herbal Products	St. John's Wort (*Hypericum perforatum)*	Co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of

		therapeutic effect and development of resistance.
HMG Co-A Reductase Inhibitor	Lovastatin, Simvastatin	There may be potential for serious reactions such as myopathy including rhabdomyolysis.
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 atazanavir 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	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Protease Inhibitor	Indinavir	Atazanavir and indinavir are associated with hyperbilirubinaemia. Co-

		administration of ZANRIT and indinavir is not recommended (see section 4.5).
Proton pump inhibitors	Omeprazole	Co-administration may reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.

4.4 Special warnings and precautions for use

The risk of HIV transmission to others

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

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia. Combination antiretroviral therapy has also been associated with the redistribution/accumulation of body fat, including 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.

Lipid disorders, weight and metabolic parameters

Treatment with ritonavir as in ZANRIT 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 – Table 2 for additional information on potential medicine interactions with ritonavir and HMG-CoA Reductase Inhibitors (hypolipidemics).

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART).

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, cytomegalovirus retinitis, and cryptococcal meningitis, *Mycobacterium avium* infection, cytomegalovirus, or *Pneumocystis jiroveci* (carinii) pneumonia.

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 disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

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

Allergic reactions, rash, and associated syndromes

Ritonavir: Allergic reactions including urticaria, skin eruptions, bronchospasm, and angioedema have been reported. Rare cases of anaphylaxis and Stevens-Johnson syndrome have also been reported.

Atazanavir: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with ZANRIT. In most patients, rash resolves within 2 weeks while continuing therapy. ZANRIT should be discontinued if severe rash develops. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions including Drug Rash, Eosinophilia, and Systemic Symptoms (DRESS) syndrome have been reported in patients taking atazanavir.

Hepatic impairment and toxicity

Atazanavir and ritonavir are principally metabolised by the liver; caution should be exercised when administering ZANRIT to patients with hepatic impairment because both atazanavir and ritonavir concentrations may be increased, in some cases up to five times

the upper limit of normal. Clinical hepatitis and jaundice have occurred (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 ZANRIT to patients with pre-existing mild liver disease, liver enzyme abnormalities or hepatitis.

Increased AST/ALT monitoring should be considered in these patients during the first three months of ZANRIT treatment. There have been reports of hepatic dysfunction, including fatalities, particularly in patients taking multiple concomitant medicines and/or with advanced AIDS. ZANRIT is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia, with fatalities having been observed in some cases. Patients with advanced HIV disease may be at increased 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 should occur. Patients who exhibit these signs or symptoms should be evaluated and ZANRIT therapy should be discontinued if a diagnosis of pancreatitis is made.

Diabetes mellitus/hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustment of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In patients who discontinued protease inhibitor therapy, the hyperglycaemia persisted in some cases.

Corticosteroids

Concomitant use of ritonavir and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate. Similar findings with concomitant administration of ritonavir and other inhaled corticosteroids that are metabolised similarly to fluticasone, such as budesonide, cannot be excluded. Particular caution should be used when administering ZANRIT and any of these inhaled or intranasally administered glucorticoids (see section 4.5 – Table 2).

PDE5 Inhibitors

Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction or pulmonary hypertension in patients receiving ZANRIT. Co-administration of ZANRIT with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as

hypotension and prolonged erection. Concomitant use of sildenafil with ZANRIT is contraindicated in pulmonary arterial hypertension patients (see Section 4.3).

Herbal Products

Patients on ZANRIT should not use products containing St. John's Wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of ritonavir. This may result in loss of therapeutic effect and development of resistance (see IRIS and section 4.3).

HMG-CoA Reductase Inhibitors

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ZANRIT with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis.
Caution must be exercised, and reduced doses should be considered if ZANRIT is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5 – Table 2).

Resistance/Cross-Resistance

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

Hyperbilirubinemia

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving atazanavir. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving ZANRIT should be evaluated for alternative aetiologies. No long-term safety data are available for patients experiencing persistent elevations in bilirubin >5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to ZANRIT may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of ZANRIT is not recommended since long-term efficacy of reduced doses has not been established.

Laboratory Tests

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

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For comprehensive information concerning laboratory test alterations associated with nucleoside analogues, the healthcare professional should refer to the complete product information for each of these 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.

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In most reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has been postulated, although mechanism of action has not been established.

PR Interval prolongation

ZANRIT has the potential to prolong the PR interval of the electrocardiogram in some patients. Reports of second-or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported. ZANRIT should be used with caution in patients with pre-existing conduction system disease. Caution should be used when co-administering ZANRIT with medicines known to induce PR interval prolongation.

Cholelithiasis

Cholelithiasis has been reported in patients receiving atazanavir (see section 4.8). Some patients required hospitalization for additional management and some had complications. If signs or symptoms of cholelithiasis occur, temporary interruption or discontinuation of treatment may be considered.

Nephrolithiasis

Cases of nephrolithiasis have been reported during post-marketing surveillance in HIV-infected patients receiving ZANRIT therapy. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered.

Renal disease

Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment (see also section 4.2). Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8).

Chronic kidney disease in HIV-infected patients treated with atazanavir, with or without ritonavir, has been reported during post-marketing surveillance. A large prospective observational study has shown an association between an increased incidence of chronic kidney disease and cumulative exposure to atazanavir/ritonavir-containing regimen in HIV-infected patients with an initially normal eGFR. This association was observed independently of exposure to tenofovir disoproxil. Regular monitoring of the renal function of patients should be maintained throughout the treatment duration (see section 4.8).

Elderly

Safety and efficacy have not been established in the elderly.

ZANRIT *contains lactose*

ZANRIT contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

ZANRIT has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP34A> CYP206> CYP2C9> CYP2C19 >> CYP2A6, CYP1A2, CYP2E1.

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There is some evidence that ZANRIT may increase the activity of glucuronosyl glucuronyl transferase; and therefore, loss of therapeutic effects from directly glucuronidated medicines during ZANRIT therapy may signify the need for dosage adjustments 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 ZANRIT. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir, as contained in ZANRIT. Dosage reductions may be required for those medicines extensively metabolised by CYP3A.

There have been reports of cardiac and neurologic events when ritonavir, as contained in ZANRIT, has been co-administered with disopyramide, mexiletine, nefazodone or fluoxetine. The possibility of medicine interaction cannot be excluded.

Table 2

Potential Effects on Medicines co-administered with ritonavir

Medicine Category Representative Medicines by Potential Interaction Category

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	Contra-Indicated Medicines	**Large[1] ↑AUC[2] (CYP3A)**	**Moderate[1] ↑AUC[2] (CYP2D6)**	**Moderate[1] ↑ Or ↓AUC[2] (CYP2C9/19)**	**Possible ↓AUC[2] (Unknown CYP)**	**Possible AUC[2] (glucuronidation**			
Analgesics, Narcotics		Alfentanil Fentanyl	Hydrocodone Oxycodone Propoxyphene Tramadol		Levamethadyl (LAAM)	Codeine Hydromorphone Pethidine Methadone* Morphine			

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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-asthmati						Theophylline*

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Antibiotic, Macrolide		Erythromycin	Clarithromycin*			
Antibiotic, Steroidal		Fusidic acid				
Anticonvulsant		Carbamazepine	Clonazepam		Phenobarbitone	Valproate Ethosuximide

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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]	

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Antimycobacterial		Rifabutin*			Ethionamide Rifampicin	
Antiparasitics		Quinine		Proguanil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine Trimetrexate	Atovaquone
Antiulcer Agents				Lansoprazole Omeprazole		

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Beta-blockers Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Verapamil	Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betazol[1]	

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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] Methysergide[11]	
Haemorheologic agent					Pentoxifylline	

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HIV Antivirals		Indinavir* Saquinavir*			Nevirapine[11]	
Hypoglycaemics				Glimepiride Glipizide Glyburide Tolbutamide		
Hypolipidaemics		Atorvastatin Lovastatin Simvastatin			Gemfibrozil	Clofibrate

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Immuno-suppressants		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 Oestradiol*
Stimulants				Dexfenfluramine Methamphetamine	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

Ritonavir interactions and co-administration recommendations

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 Cr Cl 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 ZANRIT and digoxin will result in significantly increased digoxin levels and related side effects. Digoxin is contraindicated in patients taking ZANRIT.

Inhaled/nasal corticosteroid:

Concomitant use of ZANRIT 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 ZANRIT, was co-administered with inhaled or intranasally administered fluticasone propionate.

These effects could also occur with other corticosteroids metabolised via the cytochrome P450 3A pathway, e.g. budesonide. Therefore, concomitant use of ZANRIT 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. ZANRIT should not be co-administered with fusidic acid.

Hypericum perforatum (St. John's Wort):

Patients on ZANRIT 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. Co-administration 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.

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Ketoconazole:

Concomitant administration of ritonavir (500 mg every 12 hours) and ketoconazole (200 mg four times daily) resulted in an increase of mean ketoconazole AUC_{24} and by 244 % and 55 %, respectively. The mean half-life of ketoconazole increased from 2,7 to 13,2 hours. 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 ZANRIT with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered.

Nelfinavir:

Interactions between ZANRIT 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:

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A pharmacokinetic study demonstrated that the concomitant administration of ZANRIT 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 ZANRIT 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.

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Sildenafil:

PDE5-inhibitors (including sildenafil) are contraindicated for concomitant use with ZANRIT. 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.

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Trazodone:

Concomitant use of ZANRIT 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.

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Interactions and effects on AUC and C_{max} of co-administration with ritonavir as shown in Table 3 below:

Table 3

Effect on ritonavir AUC and C_{max} with **co-administration of ritonavir with other medicines**

Medicine	**Ritonavir Dosage**	**n**	**AUC % (95 CI)**	**Cmax % (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 %)	

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Rifampicin 600 mg or 300 mg daily 10 days1	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:

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 ZANRIT 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 ZANRIT and substances that inhibit CYP3A4 may increase atazanavir plasma concentrations. The magnitude of CYP3A4- mediated medicine interactions (effect on atazanavir as contained in ZANRIT or effect on co- administered medicines) may change when atazanavir as contained in ZANRIT is co- administered with ritonavir, a potent CYP3A4 inhibitor.

Caution should be used when co-administering atazanavir as contained in ZANRIT 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 ZANRIT:

Antidysrhythmics (amiodarone, systemic lidocaine and quinidine):

Contra-indicated if atazanavir as in ZANRIT is co-administered with ritonavir as in ZANRIT 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 ZANRIT 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 ZANRIT, 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 ZANRIT may increase rifabutin plasma concentrations.

Antineoplastic:

Irinotecan: Atazanavir as contained in ZANRIT 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.

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Ergot derivatives:

Dihydroergotamine, ergotamine, ergonovine, methylergonovine: Contra-indicated 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: Contra-indicated 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 ZANRIT. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including ZANRIT, are used in combination with atorvastatin. Concomitant administration is contraindicated.

Neuroleptic:

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

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Protease inhibitor:

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

Saquinavir: Coadministration 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 ZANRIT 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 ZANRIT, 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: Contra-indicated due to potential for increased concentrations of the sedative hypnotic and increased risk of prolonged sedation or respiratory depression.

Herbal medicines: St. John’s Wort (*Hypericum perforatum*):

Patients taking atazanavir as contained in ZANRIT 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.

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Nucleoside reverse transcriptase inhibitors (NRTIs):

Didanosine: Co-administration of didanosine buffered tablets and atazanavir as contained in ZANRIT 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 ZANRIT (see section 4.2: Concomitant therapy). Atazanavir as contained in ZANRIT increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir- associated adverse events, including renal disorders. Patients receiving ZANRIT 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 ZANRIT (see section 4.2).

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

Other:

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

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

Anticoagulants:

Warfarin: The co-administration of warfarin with ZANRIT 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 ZANRIT 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 ZANRIT 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 ZANRIT, 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 ZANRIT.

Voriconazole: Should not be administered to patients receiving ZANRIT.

Erectile dysfunction agents:

Phosphodiesterase (PDE5) inhibitors (e.g. sildenafil, tadalafil, or vardenafil): Co-administration of ZANRIT 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.

H_2-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 ZANRIT.

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

Macrolide antibiotics:

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

Oral contraceptives:

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

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

Pregnancy

ZANRIT is contraindicated in pregnancy, as safety has not been established.

Breastfeeding

ZANRIT is contraindicated during breastfeeding (see section 4.3). 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 breast-feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines:

ZANRIT may influence the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with ZANRIT affects them, as nervous system side effects such as dizziness, somnolence, disorientation, blurred vision and syncope have been reported in patients taking atazanavir/ritonavir.

4.8 Undesirable effects

a). Summary of the safety profile

The most frequent reported clinical adverse events, other than asthenia, among patients receiving ritonavir were gastrointestinal and neurological disturbances including nausea, diarrhoea, vomiting, anorexia, abdominal pain, taste perversion and circumoral and peripheral paraesthesias.

The more frequent adverse events of any severity with at least a possible relationship to regimens containing atazanavir and one or more NRTIs were nausea (20 %), jaundice (13 %), and diarrhoea (10 %). Among patients receiving atazanavir 300 mg with ritonavir 100 mg, (as in ZANRIT) the frequency of jaundice was 19 %. Jaundice was reported within a few days to a few months after the initiation of treatment and resulted in discontinuation of treatment in < 1 % of patients.

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

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

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

b). Tabulated summary of adverse reactions Atazanavir alone and in combination i.e. as in ZANRIT:

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Hypersensitivity, allergic reaction

Metabolism and nutrition disorders	Less frequent Frequency unknown	Anorexia, increased appetite, decreased weight, weight gain Hyperglycaemia, diabetes mellitus
Psychiatric disorders	Less frequent	Anxiety, depression, sleep disorder, insomnia, abnormal dreams, disorientation, confusion
Nervous system disorders	Frequent Less frequent	Headache, dizziness Peripheral neurologic symptoms, amnesia, somnolence, dysgeusia, syncope, abnormal gait
Eye disorders	Frequent	Ocular icterus
Cardiac disorders	Less frequent Frequency unknown	Oedema, palpitations, QTc prolongation, Torsades de Pointes Second-degree AV block*, third-degree AV block*

Vascular disorders	Less frequent	Hypertension, syncope
Respiratory, thoracic, and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting Dry mouth, flatulence, gastritis, pancreatitis, stomatitis aphthous, abdominal distension
Hepato-biliary disorders	Frequent Less frequent	Jaundice Hepatitis, hepatosplenomegaly, cholelithiasis, cholestasis, cholecystitis

Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash Alopecia, pruritus, urticaria, DRESS (medicine rash with eosinophilia and systemic symptoms) syndrome, angioedema, vasodilatation, vesiculobullous rash, eczema, Stevens-Johnson syndrome, eruptions
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, muscle atrophy, myalgia, myopathy
Renal and urinary disorders	Less frequent	Haematuria, pollakiuria, proteinuria, nephrolithiasis, interstitial nephritis, kidney pain, chronic kidney disease
Reproductive system and breast disorders	Less frequent	Gynaecomastia

General disorders and administrative site conditions	Frequent	Fatigue, lipodystrophy syndrome
	Less frequent	Chest pain, pyrexia, malaise, gait disturbance, asthenia

c). Tabulated summary of adverse reactions - Ritonavir

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Pharyngitis

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Blood and lymphatic system disorders	Frequent	Decreased white blood count, decreased haemoglobin, decreased neutrophils, increased eosinophils
	Less frequent	Anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, increased neutrophils, increased white blood counts, increased prothrombin time
	Frequency unknown	Thrombocytopaenia
Immune system disorders	Frequent	Allergic reactions including urticaria, face oedema
	Less frequent	Anaphylaxis, Stevens-Johnson syndrome
Endocrine disorders	Less frequent	Diabetes mellitus

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Metabolism and nutrition disorders	Frequent	Anorexia, hyperlipaemia, weight loss
		Hyperglycaemia, diabetes mellitus, avitaminosis, cachexia, dehydration*, oedema, glycosuria, gout, hypercholesterolaemia, peripheral oedema, redistribution/accumulation of body fat (see section 4.4)
	Less frequent	Hypertriglyceridaemia, hyperuricaemia
	Frequency unknown	

Psychiatric disorders	Frequent Less frequent	Anxiety Agitation, confusion, depression, emotional liability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking
Nervous system disorders	Frequent Frequency unknown	Circumoral paraesthesia, headache, peripheral paraesthesia, taste perversion, dizziness, hyperaesthesia, paraesthesia, somnolence Seizure, syncope, abnormal dreams, amnesia, aphasia, ataxia, convulsion, grand mal convulsion, inco- ordination, 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 Frequency unknown	Palpitations, syncope Tachycardia, myocardial infarction
Vascular disorders	Frequent Less frequent	Vasodilation Haemorrhage, hypotension including orthostatic hypotension, migraine, peripheral vascular disorder, postural hypotension

Respiratory, thoracic and mediastinal disorders	Frequent	Increased cough, pharyngitis
	Less frequent	Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder and rhinitis
Gastrointestinal disorders	Frequent	Abdominal pain, diarrhoea, nausea, vomiting, dry mouth, dyspepsia, eructation, flatulence, local throat irritation, mouth ulcer, anorexia
	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

Hepato-biliary disorders	Frequent	Cholangitis, hepatitis (including increased AST, ALT GGT), hepatomegaly, liver damage, blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Frequent	Maculopapular rash, pruritus, rash, sweating, lipodystrophy,
	Less frequent	Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), acne, contact dermatitis, dry skin, eczema, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea, urticaria, vesiculobullous rash

Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Myalgia Arthralgia, arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness, myositis, neck pain, neck rigidity, twitching, rhabdomyolysis, myopathy/CPK increased
Renal and urinary disorders	Less frequent Frequency unknown	Dysuria, haematuria, kidney calculus, kidney failure, kidney pain, nocturia, polyuria, pyelonephritis, urethritis, urinary frequency, urinary retention Acute renal failure

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Reproductive system and breast disorders	Less frequent Frequency unknown	Impotence, penis disorder Menorrhagia
General disorders and administrative site conditions	Frequent Less frequent	Asthenia, fever, pain, weight loss Abnormal gait, chest pain, chills, flu syndrome, malaise, substernal chest pain
Investigations	Frequent Less frequent	Abnormal liver function tests Abnormal electro-oculogram, abnormal electroretinogram, altered hormone level
Injury and poisoning	Less frequent	Accidental injury, hypothermia
Surgical and medical procedures	Frequent	Vasodilation

d). Description of selected adverse reactions

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

Metabolic parameters

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

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases, fatalities have been observed.

Patients with advanced HIV disease

may be at risk of elevated triglycerides and pancreatitis

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

Rash and associated syndromes

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with atazanavir. Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with the use of atazanavir

e) Other special populations

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

The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between ritonavir (as in ZANRIT) and comparator regimens.

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 online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

In overdose with ZANRIT side effects of both atazanavir and ritonavir can be precipitated and/or be of increased severity.

Signs and symptoms

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Atazanavir

Human experience of acute overdose with atazanavir is limited.

At high doses that lead to high medicine exposure, the side effects of atazanavir may be precipitated and/or be of increased severity. Jaundice, predominantly 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. Paraesthesias and renal failure with eosinophilia have been reported with ZANRIT overdose.

Management of overdose

There is no specific antidote for overdose with ZANRIT. Treatment of overdose with ZANRIT should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. It is proposed that management of overdose could also entail and administration of activated charcoal. Since ZANRIT is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors

ATC code: J05AR26

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Mechanism of action

Ritonavir

Ritonavir dosed as a pharmacokinetic enhancer

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A-mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor 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.

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

In vitro data indicate that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of ritonavir that inhibits 50 % and 90 % of viral replication in vitro in plasma-free surroundings is approximately 0,02 µm and 0,11 µm, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines, showed no direct toxicity at concentrations up to 25 µm, with a resulting in vitro therapeutic index of at least 1000.

Ritonavir-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to ritonavir and genotypic analysis showed that the resistance was attributable primarily to specific amino acid substitutions in the HIV-1 protease at codons V82F, I84V, A71V and M46I. Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase I/II trials. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at positions 82 (Val to Ala/Phe), 54 (Ile to Val), 71 (Ala to Val/Thr) and 36 (Ile to Leu), followed by combinations of mutations at an additional 5 specific amino acid positions. Viral strains isolated *in vivo* without a change at codon 82 did not have decreased susceptibility to ritonavir. The 82- mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to five-fold decrease in viral sensitivity *in vitro* from baseline.
The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from five patients were also tested for cross-resistance to amprenavir and

nelfinavir; isolates from two patients had a decrease in susceptibility to nelfinavir (12 to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested *in vitro* retained full susceptibility to ritonavir.

Atazanavir

Atazanavir (ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.
No substantial differences were observed between the pharmacokinetics of healthy adult volunteers and in HIV–infected patients.

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

Resistance in vitro

Atazanavir susceptibility was evaluated in clinical isolates from patients without prior atazanavir exposure and exhibiting a wide array of genotypic and phenotypic patterns. There was a clear trend toward decreased susceptibility to atazanavir as isolates exhibited high resistance levels to multiple protease inhibitors. In general, susceptibility to atazanavir was retained among isolates resistant to 1 - 2 protease inhibitors, despite the presence of primary substitutions associated with resistance to protease inhibitors.

Resistance in vivo

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

Treatment-naïve patients

In a study of treatment-naïve patients comparing the efficacy of atazanavir plus ritonavir (as in ZANRIT) to lopinavir plus ritonavir, after 96 weeks of treatment, of the 30 isolates from patients with virologic failure without baseline substitutions, only 1/28 displayed phenotypic resistance to ATV (> 5,2) with multiple PI substitutions (L10F, V32I, K43T, M46I, A71I, G73S, I85I/V, and L90M) without emergence of I50L.

Treatment-experienced patients

Approximately 80 % and 100 % of atazanavir-resistant isolates from experienced patients treated with atazanavir or the combination of atazanavir plus saquinavir, respectively, showed no evidence of the emergence of the I50L substitution, instead displaying decreased susceptibility to multiple protease inhibitors, which coincided with the accumulation of several additional amino acid substitutions, including I84V.
In studies of treatment-experienced patients treated with ATV/RTV most ATV-resistant isolates from patients who experienced virologic failure through 48 weeks developed substitutions that were associated with resistance to multiple PIs and displayed decreased susceptibility to multiple PIs. The most common protease substitutions (> 10 % frequency) to develop in the viral isolates of patients who failed treatment with ATV 300 mg once daily and RTV 100 mg once daily (together with tenofovir and NRTI)

included L10F, K20I/M/V, V32I, M36I/L, M46I/L, I54V, A71V/T/I, G73S/T/C, and V82A/T/L. Other substitutions that developed on ATV/RTV treatment including L24I, L33F/I/V, G48V, I50L/V, I84V, and L90M occurred in less than 10 % of patient isolates.

5.2 Pharmacokinetic properties

Absorption

Ritonavir

In a single-dose pharmacokinetic study in HIV positive fasting male subjects, high levels of ritonavir were achieved and maintained for several hours after oral administration of 100 mg, 200 mg, 400 mg, 600 mg, 800 mg or 1000 mg of ritonavir. Area under the concentration-time curve (AUC) ranged from 3,92 to 123 µg.h/mL, respectively and the maximal concentration (C_{max}) ranged from 0,416 to 12,7 µg/mL.

The pharmacokinetics of ritonavir was dose-dependent with more than proportional increases in the AUC and C_{max} occurring with increasing dose. The time to maximum concentration (T_{max}) remained constant at approximately 2 – 4 hours with increasing dose. Renal clearance averaged less than 0,1 L/h and was relatively constant throughout the dosage range. There is no parenteral formulation of ritonavir therefore, the absolute bioavailability has not been determined.

Administration of a single 100 mg dose of ritonavir 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}.

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. At steady state with a 600 mg twice a day dose, C_{max} and C_{trough} values of 11,2 and 3,7 µg/mL were observed, respectively. The $t_{1/2}$ of ritonavir was approximately three to five hours. The steady-state apparent clearance in patients treated with 600 mg twice a day has averaged 8,8 ± 3,2L/h.

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

Atazanavir

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 Day 8. Administration of atazanavir sulphate with food enhances bioavailability and reduces pharmacokinetic variability.

Distribution

Ritonavir

The apparent volume of distribution (VB/F) of ritonavir is approximately 0,41 ± 0,25 L/kg after a single 600 mg dose. The protein binding of ritonavir in human plasma was noted

to be approximately 98 to 99 %. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Total plasma protein binding is constant over the concentration range of 1 to 100µg/mL.

Tissue distribution studies with ^{14}C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios of approximately one measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Atazanavir

Atazanavir is 86 % bound to human serum proteins.

Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89 % and 86 %, respectively, at 1000 ng/mL). In a multiple-dose study in HIV- infected patients dosed with 400 mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

Biotransformation

Ritonavir

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily isozyme CYP3A and to a lesser extent CYP2D6. Animal studies as well as *in vitro* experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. 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 ritonavir. However, the AUC of the M-2 metabolite was approximately 3 % percent of the AUC of ritonavir.

Atazanavir

Atazanavir is principally metabolised by the CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites.

Elimination

Ritonavir

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86 % of radiolabel was recovered in the stool. In these studies, renal elimination was not found to be a major route of elimination of ritonavir.

Atazanavir

The mean elimination half-life of atazanavir in healthy volunteers and HIV-infected adult patients was approximately 7 hours.

Following a single 400 mg dose of 14C-atazanavir, 79 % and 13 % of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged medicine accounted for approximately 20 % and 7 % of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged medicine was 7 % following 2 weeks of dosing at 800 mg once daily.

Pharmacokinetics in special patient groups

Ritonavir

***Effects on Electrocardiogram**:* QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95 % upper confidence bound) difference in QTcF from placebo was 5,5 (7,6) msec for 400 mg twice-daily ritonavir. The Day 3 ritonavir exposure was approximately 1,5- fold higher than that observed with the 600 mg twice-daily dose at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. Maximum PR interval was 252 msec and no second -or third- degree heart block was observed.

***Renal Impairment**:* Currently, there are no data specific to this patient population. However, because ritonavir is highly protein it is unlikely that ritonavir will be significantly removed by haemodialysis or peritoneal dialysis.

***Hepatic Impairment**:* In six HIV-infected adult subjects with mild hepatic insufficiency dosed with ritonavir 400 mg twice a day, ritonavir exposures were similar to control subjects dosed with 500 mg twice a day. Results indicate that dose adjustment is not required in patients with mild hepatic impairment. Adequate pharmacokinetic data are not available for patients with moderate hepatic impairment. Protein binding of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function.

Atazanavir

Renal impairment*:* In healthy subjects, the renal elimination of unchanged atazanavir was 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 (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that

the atazanavir pharmacokinetic parameters were decreased by 30 % to 50 % in patients undergoing haemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown (see sections 4.2 and 4.4.).

Hepatic impairment: Atazanavir is metabolised and eliminated primarily by the liver. Atazanavir (without ritonavir) has been studied in adult subjects with moderate-to-severe hepatic impairment (14 Child-Pugh Class B and 2 Child Pugh Class C subjects) after a single 400 mg dose. The mean $AUC_{(0-\infty)}$ was 42 % greater in subjects with impaired hepatic function than in healthy subjects. The mean half-life of atazanavir in hepatically impaired subjects was 12,1 hours compared to 6,4 hours in healthy subjects. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).

Age/Gender: A study of the pharmacokinetics of atazanavir was performed in 59 healthy male and female subjects (29 young, 30 elderly). There were no clinically important pharmacokinetic differences based on age or gender.

Race: A population pharmacokinetic analysis of samples from Phase II clinical trials indicated no effect of race on the pharmacokinetics of atazanavir.

Pregnancy*:* Atazanavir peak concentrations and AUCs were found to be approximately 26-40 % higher during the postpartum period (4-12 weeks) than those observed historically in HIV infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2-fold higher during the postpartum period when compared to those observed historically in HIV infected non-pregnant patients.

Paediatric population

Ritonavir

The pharmacokinetic profile of ritonavir in paediatric patients below the age of two years has not been established. Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 – 14 years receiving doses ranging from 250 mg/m^2 twice a day to 400 mg/m^2 twice a day. Across dose groups, ritonavir steady-state oral clearance was approximately 1,5 times faster in paediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily.

Atazanavir

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

Colloidal silicon dioxide

Copovidone

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium stearyl fumarate

Sorbitan monolaurate

Film Coating

Opadry 03F190003 Clear consisting of HPMC 2910/hypromellose and macrogol/PEG

Methylene chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Round opaque white HDPE bottle containing 30 tablets and one 2 g silica gel sachet and a white, round, fine ribbed, non-child resistant cap, sealed by induction sealing process.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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7945, South Africa

8. REGISTRATION NUMBER

APPROVED PROFESSIONAL INFORMATION

A56/20.2.8/0800

9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

N/A