1.3.1.1 PROFESSIONAL INFORMATION

WARNING:

Co-administration of RIATEM with certain non-sedating antihistamines, sedative hypnotics, anti-dysrhythmics or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of RIATEM on the hepatic metabolism of certain medicines (see CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

SCHEDULING STATUS **S4**

PROPRIETARY NAME AND DOSAGE FORM

RIATEM (film-coated tablets)

COMPOSITION

RIATEM:

Each film-coated tablet contains Atazanavir sulphate equivalent to Atazanavir 300 mg and Ritonavir 100 mg

RIATEM contains the following inactive ingredients:

- Colloidal Silicone Dioxide
- Copovidone
- Crospovidone
- Lactose Monohydrate
- Magnesium Stearate
- Microcrystalline Cellulose
- Polysorbate 80

- Sodium Stearyl Fumarate
- Sorbitan Monolaurate.

The film-coating of **RIATEM** contains:

- Hypromellose
- Titanium dioxide (CI 77891)
- Macrogol/PEG
- Talc
- Iron oxide yellow (CI 77492)
- Polysorbate 80

RIATEM contains sugar: lactose monohydrate 164,36 mg

CATEGORY AND CLASS

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

RIATEM is a fixed dose combination of the HIV protease inhibitors **atazanavir sulphate** and **ritonavir**.

Atazanavir sulphate component:

Atazanavir sulphate is an azapeptide HIV-1 protease inhibitor, with a C_2–symmetrical chemical structure that is active against HIV-1 and HIV-2.

Ritonavir component:

Ritonavir is a peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases.

Pharmacokinetic properties:

Atazanavir Sulphate component:

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

Absorption:

After oral administration, peak concentrations occur 2 to 2,5 hours after dosing. Steady state is achieved between day 4 and day 8 of dosing. On multiple dosing with a ritonavir-boosted regimen, peak plasma concentrations are achieved after 3 hours. Atazanavir absorption is sensitive to food. Bioavailability of atazanavir sulphate (with or without the ritonavir boosted regimen) is enhanced if given with food and pharmacokinetic variability is reduced (see **DOSAGE AND DIRECTIONS**).

Distribution:

Atazanavir is 86 % bound to human serum proteins. It is present in CSF at less than 3 % of plasma concentrations but has excellent penetration into seminal fluid.

Metabolism:

Atazanavir is principally metabolised by the CYP3A4 isoenzyme to oxygenated metabolites.

Elimination:

Atazanavir metabolites are excreted in the bile as either free or glucuronidated metabolites. Only 7 % of the parent substance is excreted unchanged in the urine.

Microbiology:

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

There is a clear trend toward decreased susceptibility to atazanavir in patients with high resistance levels to multiple protease inhibitors. The primary atazanavir resistance mutation occurs at HIV protease codon 50 and confers about a 9-fold decrease in susceptibility (known as the isoleucine-to-leucine substitution: I50L). Sensitivity to atazanavir is affected by various primary and secondary mutations that accumulate in patients who have failed other HIV protease inhibitors, with high-level resistance more

likely if five or more additional mutations are present (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Ritonavir:

The pharmacokinetics of ritonavir is dose-dependent; with more than proportional increases in the AUC and C_{max} occurring with increasing dose. The time to maximum concentration (T_{max}) remains constant at approximately 2-4 hours with increasing dose. Renal clearance is limited and is relatively constant with increasing dosage.

Absorption:

Ritonavir is absorbed after oral administration and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food and is dose related.

Distribution:

Ritonavir is highly bound to plasma proteins (approximately 98 % to 99 %), mainly human serum albumin (HAS) and alpha1-acid glycoproteins (AAG). Penetration of ritonavir into the CNS is minimal.

Metabolism:

Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Ritonavir primarily undergoes oxidative metabolism. Five metabolites have been identified in human urine and faeces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent medicine, but concentrations in plasma are low (AUC of the M-2 metabolite is approximately 3 % of the AUC of the parent medicine).

Elimination:

Ritonavir is eliminated mainly via the hepatobiliary system. About 86 % of a dose is eliminated through the faeces (both as unchanged medicine and as metabolites) and about 11 % is excreted in the urine (3,5 % as unchanged medicine). Thus renal elimination is not a major route of elimination of ritonavir. The elimination half-life ($t_{1/2}$) is approximately 3 to 5 hours.

Special Populations:

- **Mild hepatic impairment:**

  Since the liver is the main organ of elimination of ritonavir, hepatic impairment may affect the pharmacokinetics of ritonavir. Caution should be exercised when administering this medicine to patients with impaired liver function and liver enzyme values monitored. **(see WARNINGS AND SPECIAL PRECAUTIONS).**

- **Moderate and severe hepatic impairment:**

  Is contraindicated for use (see **CONTRAINDICATIONS and DOSAGE and DIRECTIONS-Special Populations**).

- **Smoking:**

  AUC is reduced in smokers compared to non smokers.

Microbiology:

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

Ritonavir in **RIATEM** is used as a pharmacokinetic enhancer (CYP34 inhibitor) and the low doses used for this purpose are not known to induce ritonavir resistance mutations.

INDICATIONS

RIATEM is indicated in:

- Combination with other antiretroviral medicines for the treatment of patients with HIV infection when therapy is warranted.

CONTRAINDICATIONS

RIATEM is contraindicated for use in:

- Patients with a known hypersensitivity to atazanavir, ritonavir or to any of the components used in **RIATEM** (see **COMPOSITION**).

- Patients with moderate to severe hepatic insufficiency (see **Pharmacokinetics-Special populations and WARNINGS AND SPECIAL PRECAUTIONS and DOSAGE and DIRECTIONS-Special Populations**).
- Patients concomitantly taking anti-tuberculosis regimens containing rifampicin.
- Patients concomitantly taking medicines that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening diseases. These medicines include: **anti-dysrhythmics** (e.g. digoxin, amiodarone, bepridil, flecainide, encainide, propafenone and quinidine), **anti-histamines**, **ergot alkaloids** (e.g. dihydroergotamine, ergometrine, ergotamine, ergonovine, methylergonovine), **gastro-intestinal prokinetics** (e.g. cisapride), **antipsychotics** (e.g. pimozide), **sedatives and hypnotics** (e.g. triazolam and midazolam), **antifungals** (e.g. ketoconazole, itraconazole and voriconazole) and **statins** (e.g. lovastatin and simvastatin) (see **BOXED WARNING ABOVE PROFESSIONAL INFORMATION and BELOW and WARNINGS AND SPECIAL PREACUATIONS and INTERACTIONS**).
- Patients concomitantly using products containing St. John's wort (*Hypericum perforatum* [see **WARNINGS AND SPECIAL PREACUATIONS and INTERACTIONS**]).
- Patients who are old since the safety and efficacy in elderly patients has not been established.
- Patients who are pregnant or lactating (see **HUMAN REPORODUCTION**).

Ritonavir:

- Ritonavir is a potent inhibitor of many cytochrome P450 mediated bio-transformations and may produce large increases in the plasma concentration of certain medicines (see **CONTRAINDICATIONS ABOVE**). These medicines have recognised risks of dysrhythmias, haematologic abnormalities, seizures or other potentially serious adverse effects.

- Additionally, acute ergot toxicity characterised by peripheral vasospasm and ischemia of the extremities may be associated with the co-administration of ritonavir and ergotamine or dihydroergotamine. The frequency of this is unknown.

- Ritonavir has the potential to produce large increases in highly metabolised sedatives and

hypnotics like midazolam and triazolam, and may produce extreme sedation and respiratory depression when co-administered.

WARNINGS AND SPECIAL PRECAUTIONS

The atazanavir component of RIATEM:

Diabetes mellitus/hyperglycaemia:

New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycaemia and diabetic ketoacidosis may occur in HIV-infected patients receiving protease inhibitor therapy such as atazanavir but the frequency is unknown.

Some patients require either initiation or dose adjustment of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis may occur. Hyperglycemia may still persist in some patients who discontinue protease inhibitor therapy.

The frequency of these events is unknown and a causal relationship between protease inhibitor therapy and these events has not been established.

The ritonavir component of RIATEM:

Allergic Reactions:

Allergic reactions including urticaria, skin eruptions, bronchospasm, angioedema, anaphylaxis and Stevens-Johnson syndrome may occur but the frequency is unknown.

Hepatic Reactions:

Hepatic transaminase elevations exceeding five times the upper limit of normal, clinical hepatitis and jaundice may occur in patients receiving **RIATEM** alone or in combination with other antiretroviral medicines.

There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C.

Therefore, caution should be exercised when administering **RIATEM** to patients with pre-existing mild liver disease, liver enzyme abnormalities or hepatitis (see **CONTRAINDICATIONS**).

Increased AST/ALT monitoring should be considered in these patients especially at baseline during the first three months of **RIATEM** treatment.

Hepatic dysfunction, including fatalities may occur, particularly in patients taking multiple concomitant medications and/or with advanced AIDS.

RIATEM is contraindicated in patients with moderate to severe hepatic insufficiency (see **Pharmacokinetics in Special Populations and CONTRAINDICATIONS and Dosage and Directions**).

Pancreatitis:

Pancreatitis may occur in patients receiving **RIATEM** therapy, including those who develop hypertriglyceridemia. Fatalities may occur. 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 therapy with **RIATEM** should be discontinued if a diagnosis of pancreatitis is made.

Corticosteroids:

Concomitant use of **RIATEM** 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 may occur when **RIATEM** is co-administered with inhaled or intranasally administered fluticasone propionate.

Similar findings with concomitant administration of **RIATEM** and other inhaled corticosteroids that are metabolised similarly to fluticasone, such as budesonide, cannot be excluded.

Particular caution should be used when administering **RIATEM** and any of these inhaled or intranasally administered glucorticoids (see **INTERACTIONS**).

Erectile Dysfunction medicines:

Caution should be used when prescribing sildenafil, tadalafil or vardenafil to patients receiving **RIATEM**. Co-administration with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as hypotension and prolonged erection.

Herbal Products:

Patients on **RIATEM** 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 **CONTRAINDICATIONS AND INTERACTIONS**).

HMG-CoA Reductase Inhibitors:

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP34A for metabolism, thus concomitant use of **RIATEM** with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis (see **CONTRAINDICATIONS**). Caution must be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

RIATEM (atazanavir boosted ritonavir):

Lipodystrophy and metabolic abnormalities:

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

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 (ART). 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. 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 (ART).

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

The risk of HIV transmission to others:

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

Nephrolithiasis:

Nephrolithiasis may occur in patients receiving **RIATEM** (see **SIDE-EFFECTS**). If signs or symptoms of neprolithiasis occur, temporary interruption or discontinuation of treatment may be considered (see **SIDE-EFFECTS**).

Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus:

Treatment-emergent hepatitis or transaminase elevations in co-infected patients may occur.

Haemophilia:

Increased bleeding, including spontaneous skin haematomas and haemarthrosis may occur in patients with haemophilia type A and B that are treated with protease inhibitors like **RIATEM**. In some patients additional factor VIII can be given, but treatment with protease inhibitors is mostly continued or re-introduced.

PR Interval:

RIATEM has the potential to prolong the PR interval of the electrocardiogram and asymptomatic first-degree atrioventricular block may occur in some patients. **RIATEM** should be used with caution in patients with pre-existing conduction disorders. Caution should be used when co-administering **RIATEM** with any medicine that is known to induce PR interval prolongation (see **INTERACTIONS**).

Rash:

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

Hepatic Impairment and Toxicity:

RIATEM is principally metabolised by the liver. When administering **RIATEM** to patients with hepatic impairment, caution should be exercised as **RIATEM** concentrations may be increased (see **Pharmacokinetics in Special Populations** and **CONTRAINDICATIONS and DOSAGE and DIRECTIONS for use: Special Populations**).

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.

Hyperbilirubinaemia:

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) occurs commonly. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving **RIATEM** 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 should be considered if jaundice or sclera icterus associated with bilirubin elevations is of cosmetic concern to the patient. Dose reduction of **RIATEM** is not recommended since long-term efficacy of reduced doses has not been established.

Laboratory Findings:

Atazanavir sulphate component:

Adult patients:

The most frequently reported laboratory abnormality in patients receiving regimens containing the atazanavir component of **RIATEM** and one or more NRTIs is elevated total bilirubin. Other clinical laboratory abnormalities reported include: elevated amylase, elevated creatine kinase (CK), elevated ALT/SGPT, low neutrophils, elevated AST/SGOT and elevated lipase.

Ritonavir component:

The ritonavir component of **RIATEM** may be associated with alterations in

triglycerides, ALT, AST, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating **RIATEM** 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 complete professional information for each of these medicines.

Lipid Disorders:

Treatment with the ritonavir component of **RIATEM** therapy in combination with saquinavir may result in substantial increases in the concentration of total triglycerides and cholesterol (see also **INTERACTIONS**-saquinavir).

Triglyceride and cholesterol testing should be performed prior to initiating

RIATEM therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate (see **TABLE 1** for additional information on potential medicine interactions with **RIATEM** and HMG-CoA reductase inhibitors [hypolipidemics]).

Resistance/Cross-Resistance:

Varying degrees of cross-resistance among protease inhibitors may occur.

Continued administration of **RIATEM** therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors (see **Pharmacokinetics-Cross resistance**).

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

Ability to drive and use machines:

There are no specific studies about the ability to drive vehicles and use machinery. **RIATEM** may cause dizziness, impaired-concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Lactose:

Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take **RIATEM**.

INTERACTIONS

RIATEM (which contains atazanavir boosted by ritonavir) is metabolised in the liver by the cytochrome P450 enzyme system, and is an inhibitor of CYP3A4 (cytochrome P450 3A4).

- Co-administration of **RIATEM** together with medicines that are primarily **metabolised** by CYP3A4 (e.g. calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors) may result in increased plasma concentrations of the other medicine, which could increase or prolong both its therapeutic and adverse effects.
- Co-administration of **RIATEM** together with medicines that **induce** CYP3A4, (e.g. rifampicin) may decrease **RIATEM** plasma concentrations and thus reduce its therapeutic effect.
- Co-administration of **RIATEM** together with medicines that **inhibit** CYP3A4 may increase **RIATEM** plasma concentrations.
- When ritonavir-boosted atazanavir (**RIATEM**) is given, the medicine interaction profile for ritonavir may predominate because ritonavir is a more potent CYP3A4 inhibitor than atazanavir.

  The interactions for ritonavir should be consulted for more information on medicine interactions with ritonavir (see **INTERACTIONS-BELOW ritonavir component**).
- Caution should be used when **RIATEM** is co-administered with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, verapamil) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Medicines that should not be administered with RIATEM:

POSSIBLE INTERACTIONS DUE TO THE ATAZANAVIR COMPONENT:

HIV ANTIVIRAL MEDICINES:

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Didanosine: Co-administration of didanosine buffered tablets and the atazanavir component of **RIATEM** may markedly decrease[**s**] exposure to **RIATEM** (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Co-administration with **RIATEM** does not alter exposure to didanosine. Administration of the enteric-coated formulation of didanosine with **RIATEM** (ritonavir

boosted atazanavir) and a light meal decreases exposure to didanosine (see **DOSAGE and DIRECTIONS: Concomitant therapy**).

Nucleotide Reverse Transcriptase Inhibitor (NRTIs):

Tenofovir: Exposure to the atazanavir component of **RIATEM** may be decreased when tenofovir is co-administered with **RIATEM** (see **DOSAGE and DIRECTIONS: Concomitant therapy**). **RIATEM** increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving **RIATEM** and tenofovir should be monitored for tenofovir-associated adverse events.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Efavirenz: Exposure to the atazanavir component of **RIATEM** may be decreased when efavirenz is co-administered with **RIATEM** (see **DOSAGE and DIRECTIONS: Concomitant therapy**).

Nevirapine: Nevirapine, an inducer of CYP3A4, is expected to decrease exposure to the atazanavir component of **RIATEM**. In the absence of data, co-administration with **RIATEM** is not recommended. The co-administration of **RIATEM** (ritonavir boosted atazanavir) with zidovudine and lamivudine or with abacavir is not expected to significantly alter the exposure of the co-administered medicines.

Protease Inhibitors:

Saquinavir (soft gelatin capsules): Exposure to saquinavir may be increased when it is co-administered with the atazanavir component of **RIATEM**. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, has not been established.

Ritonavir: Exposure to the atazanavir component of **RIATEM** may be increased.

Indinavir: **RIATEM** and indinavir may be associated with indirect (unconjugated) hyperbilirubinaemia due to inhibition of UGT**.** Co-administration of the atazanavir component of **RIATEM** and indinavir is not recommended.

Other protease inhibitors:

The co-administration of **RIATEM** (ritonavir boosted atazanavir) with other protease inhibitors would be expected to increase exposure to the other protease inhibitors and is not recommended.

OTHER MEDICINES:

Antidysrhythmics:

Lidocaine (systemic): Concentrations may be increased when co-administered with the atazanavir component of **RIATEM**. Caution is advised and therapeutic concentration monitoring is recommended.
Amiodarone and Quinidine: Is contraindicated with **RIATEM** (due to the ritonavir component) due to potential for serious and/or life-threatening reactions, e.g. cardiac dysrhythmias (see **CONTRAINDICATIONS**).

Antimycobacterial:

Rifampicin: Substantially decreases plasma concentrations of the atazanavir component of **RIATEM**, which may result in loss of therapeutic effect and development of resistance.

Rifabutin:

Exposure to rifabutin may be increased when it is co-administered with the atazanavir component of **RIATEM**. A rifabutin dose reduction of up to 75 % (e.g. 150 mg every other day or 3 times per week) is recommended.

Antineoplastic:

Irinotecan: The atazanavir component of **RIATEM** inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities. Patients should be closely monitored for adverse events related to irinotecan.

Calcium Channel Blockers:

Bepridil: Potential for serious and/or life-threatening adverse events. Contraindicated with **RIATEM** (ritonavir boosted) (see **CONTRAINDICATIONS**).

Diltiazem: Exposure to diltiazem and a metabolite, desacetyl-diltiazem, may be increased when diltiazem is co-administered with the atazanavir component of **RIATEM**. An initial dose reduction of diltiazem by 50 % should be considered, with subsequent titration as needed and electrocardiogram monitoring is recommended.

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

Verapamil: Serum concentrations of verapamil may be increased by **RIATEM** (ritonavir boosted atazanavir) due to CYP3A4 inhibition. Caution should be exercised when verapamil and **RIATEM** is co-administered.

Ergot Derivatives:

Dihydroergotamine, ergotamine, ergonovine, methylergonovine: Contraindicated concomitantly with the atazanavir component of **RIATEM,** 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 (see **CONTRAINDICATIONS**).

GI Motility Medicines:

Cisapride: Contraindicated concomitantly with **RIATEM** due to potential for serious and/or life-threatening reactions e.g. cardiac dysrhythmias (see **CONTRAINDICATIONS**).

HMG-CoA Reductase Inhibitors:

Lovastatin, simvastatin: There may be a potential for serious reactions such as myopathy including rhabdomyolysis, and co-administration with **RIATEM** is contraindicated (see **CONTRAINDICATIONS**).
Atorvastatin: Exposure to atorvastatin may be increased when it is co-administered with the atazanavir component of **RIATEM**. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including **RIATEM**, is used in combination with atorvastatin. Caution should be exercised.

Neuroleptic:

Pimozide: Contraindicated concomitantly with **RIATEM** due to potential for serious and/or life-threatening reactions e.g. cardiac dysrhythmias (see **CONTRAINDICATIONS**).

Proton-Pump Inhibitors:

RIATEM should not be administered with proton pump inhibitors due to a substantial decrease in **RIATEM** plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Sedative Hypnotics:

Midazolam and triazolam: are extensively metabolised by CYP3A4. Co-administration with **RIATEM** (ritonavir boosted atazanavir) may cause a large increase in the concentrations of these benzodiazepines and therefore an increased risk of prolonged sedation or respiratory depression (see **CONTRAINDICATIONS**).

Herbal Product:

St. John's wort (Hypericum perforatum): Patients taking **RIATEM** (ritonavir boosted atazanavir) should not use products containing St. John's wort *(Hypericum perforatum)* as co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance (see **CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS**).

Antacids and Buffered Medicines:

Reduced plasma concentrations of the atazanavir component of **RIATEM** may result if antacids, including buffered **antacids**, are administered with **RIATEM**. **RIATEM** should be administered 2 hours before or 1 hour after these medicines.

Anticoagulants:

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

Antidepressants:

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

Trazodone: Concomitant use of trazodone and the atazanavir component of **RIATEM** may increase plasma concentrations of trazodone. If trazodone is used with a CYP3A4 inhibitor such as **RIATEM**, the combination should be used with caution and a lower dose of trazodone should be considered. Adverse events of nausea, dizziness, hypotension and syncope may occur following co-administration of trazodone and the ritonavir component of **RIATEM**.

Antifungals:

Ketoconazole and itraconazole (> 200 mg/day) should not be used with **RIATEM** (ritonavir boosted atazanavir). Voriconazole should not be administered to patients receiving **RIATEM (see CONTRAINDICATIONS).**

Erectile Dysfunction Medicines:

Phosphodiesterase (PDE5) inhibitors (sildenafil, tadalafil, vardenafil): Co-administration of a protease inhibitor like **RIATEM** with a PDE5 inhibitor is expected to increase PDE5 inhibitor concentrations which may result in an increase in PDE5 inhibitor associated adverse events.

H_2-Receptor Antagonists:

When co-administered with an H_2-receptor antagonist, the recommended dose of **RIATEM** (300 mg atazanavir with ritonavir 100 mg) as a single daily dose should be given with food to all patients.

When co-administering of **RIATEM** with tenofovir and an H_2-receptor antagonist temporary separation should be considered with this dosage regimen.

Immunosuppressants:

Ciclosporin, tacrolimus, sirolimus: Exposure to ciclosporin, tacrolimus, and sirolimus may be increased when they are co-administered with the atazanavir component of **RIATEM** due to CYP3A4 inhibition. Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with **RIATEM**.

Inhaled/Nasal Corticosteroids *(interaction with ritonavir component):*

Ritonavir significantly increases plasma fluticasone propionate exposure and results in significantly decreased serum cortisol concentrations. Systemic corticosteroid effects include Cushing's syndrome and adrenal suppression. These effects could also occur with other corticosteroids metabolised via the cytochrome P4503A pathway (e.g. budesonide). Therefore, concomitant use of **RIATEM** (ritonavir boosted atazanavir) and fluticasone propionate or other glucocorticoids (that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Consider alternatives to fluticasone propionate e.g. a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone), particularly for long-term use.

Macrolide Antibiotics:

Clarithromycin: Exposure to clarithromycin may be increased when it is co-administered with **RIATEM** (ritonavir boosted atazanavir). Increased concentrations of clarithromycin may cause QTc prolongations.

Oral Contraceptives:

Ethinyloestradiol and norethindrone: Mean concentrations of ethinyloestradiol and norethindrone may increase if they are co-administered with the atazanavir component of **RIATEM.**

Decreased HDL or increased insulin resistance may be associated with increased concentrations of norethindrone, particularly in diabetic women. It is recommended that the lowest effective dose of each oral contraceptive component be used.

Alternate methods of non-hormonal contraception should be considered when **RIATEM** is taken (due to the ritonavir component).

Ethinyloestradiol and a progestin: The concentration of ethinyloestradiol is increased when co-administered with the atazanavir component of **RIATEM**, due to both UGT (glucuronosyl transferase) and CYP3A4 inhibition by the atazanavir. The net effect of **RIATEM (**ritonavir boosted atazanavir) is a decrease in the ethinyloestradiol levels, because of the inducing effect of ritonavir. The increase in progestin exposure may lead to related side-effects. When taking **RIATEM,** alternate methods of non-hormonal contraception should be considered.

POSSIBLE INTERACTIONS DUE TO THE RITONAVIR COMPONENT:

- Medicines which increase CYP34A activity (e.g. phenobarbitone, carbamazepine, dexamethasone, phenytoin, rifampicin and rifabutin) would be expected to increase the clearance of **RIATEM** resulting in decreased ritonavir plasma concentrations.
- The ritonavir component of **RIATEM** has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order:

  CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2, CYP2E1.
- The possibility exists that **RIATEM** may increase the activity of glucuronosyl transferase; thus, loss of therapeutic effects from directly glucuronidated medicines during **RIATEM** therapy may signify the need for dosage alteration of these medicines.
- In addition to the medicines listed in the **CONTRAINDICATIONS** section, **Table 1** summarises some commonly prescribed medicines, separated by the type of metabolism and expected magnitude of interaction when co-administered with **RIATEM**.
- Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with the ritonavir component of **RIATEM**.
- Dosage reduction may be required for those medicines extensively metabolised by CYP34A.
- Cardiac and neurologic events may occur when **RIATEM** is co-administered with disopyramide, mexiletine or fluoxetine.
- The possibility of interactions cannot be excluded.

TABLE 1

Potential Effects on Medicines Co-administered with RIATEM

(Contraindicated Medicines are listed in Column 1)						
Medicine Category	**Representative Medicines by Potential Interaction Category**					
	Contraindicated Medicine	**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 Tramadol		Levamethadyl (LAAM)	Codeine Hydromorphone Meperidine* Methadone* Morphine
Analgesics, non-Steroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin Piroxicam	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Anti-dysrhythmic	Amiodarone Encainide Flecainide Propafenone Quinidine	Lidocaine	Disopyramide Mexiletine		Tocainide [11]	

Antiasthmatic						Theophylline*
Antibiotic, Macrolide		Erythromycin	Clarithromycin*			
Antibiotic, Steroidal		Fusidic acid				
Anticonvulsant		Carbamazepine	Clonazepam Ethosuximide		Phenobarbitone	Divalproex Lamotrigine Phenytoin
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

Antiemetics Prokinetics	Cisapride		Dronabinol Ondansetron		Prochlorperazine [11] Promethazine	Metaclopramide
Antifungal medicines		Itraconazole Ketoconazole* Miconazole				
Antihistamines		Loratadine				
Antihypertensive				Losartan	Doxazosin [11] Prazosin [11] Terazosin [11]	
Antimycobacterial		Rifabutin*			Ethionamide Rifampicin	
Antiparasitics		Quinine		Progaunil	Albendazole Chloroquine Metronidazole Primaquine Pyrimethamine Trimetrexate	Atovaquone
Antiulcer medicines				Lansoprazole Omeprazole		
Beta-blockers			Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betaxolol[11]	

Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Verapamil				
Cancer chemo-therapeutic medicines		Tamoxifen	Etoposide Paclitaxel Vinblastine Vincristine	Cyclophos-Phamide[3] Ifosfamide[3]	Daunorubicin [11] Doxorubicin [11]	
Ergot alkaloids and derivatives	Dihydroer-gotamine Ergotamine	Bromocriptine			Ergonovine [11] Methylergonovine [11] Methysergide [11]	
Hemorheologic agent					Pentoxifylline	
HIV Antivirals		Indinavir* Saquinavir*			Nevirapine [11]	
Hypoglycaemics				Glimepiride		

				Glipzide Glyburide Tolbutamide		
Hypolipidaemics		Atorvastatin Lovastatin Simvastatin			Gemfibrozil	Clofibrate
Imuno-Suppresants		Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide		Chlorpromazine Haloperidol Perphenazine Risperidone Thioridazine			Clozapine
Sedative / hypnotics	Midazolam Triazolam	Buspirone	Clorazepate Diazepam Estazolam Flurazepam Zolpidem			Lorazepam Oxazepam Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinyl Estradiol*

Stimulants			Dexfenfluramine Methamphetamine		Methylphenidate	

1 Large = > 3X; Moderate = 1,5-3X

2 AUC = area under the plasma concentration – time curve, a measure of medicine 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 the ritonavir component of **RIATEM** may result in a statistically significant decrease in mean alprazolam C_{max} values (16 %) but not in mean AUC values (12 %). Similarly, a significant effect may occur on the sedation effect curve but not on the extent of sedation. Mild psychomotor impairment may be confounded by a learning effect. However, these pharmacokinetic and pharmacodynamic results are inconsistent when considering the pharmacologic effect of alprazolam and thus these results are not considered clinically significant.

Amprenavir:

Concentrations of the HIV-protease inhibitor, amprenavir, may increase when co-administered with the ritonavir component of **RIATEM.**

Buspirone:

Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone with medicines that potentially inhibit CYP34A, such as **RIATEM** may substantially elevate buspirone levels. When co-

administered with **RIATEM**, a dose reduction or low dose of buspirone used cautiously, is recommended.

Clarithromycin:

The concomitant administration of **RIATEM** with clarithromycin may result in a marked inhibition of the metabolism of clarithromycin due to the ritonavir component. The clarithromycin C_{max}, C_{min} and AUC may increase. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin may occur. Because of the large therapeutic window for clarithromycin, no dosage reduction is necessary in patients with normal renal function. However, for patients with renal impairment the following dosage adjustments should be considered:

For patients with creatinine clearance of 30 to 60 ml/min the dose of clarithromycin should be reduced by 50 %.

For patients with creatinine clearance < 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 **RIATEM**.

Delavirdine:

Delavirdine is an inhibitor of CYP34A-mediated metabolism. When co-administered with the ritonavir component of **RIATEM,** the plasma concentration may increase. The pharmacokinetics of delavirdine does not appear to be effected by **RIATEM** but when used in combination, a dose reduction of **RIATEM** should be considered (due to the ritonavir component).

Desipramine:

Co-administration of the ritonavir component of **RIATEM** with desipramine may result in a mean increase in the AUC of desipramine. Dosage reduction of desipramine should therefore be considered in patients taking the combination.

Didanosine:

The concomitant administration of the ritonavir component of **RIATEM** with didanosine may result in a reduction of C_{max} and AUC of didanosine. However, there is little or no effect on the pharmacokinetics

of the ritonavir component of **RIATEM**. Dose alteration of didanosine during concomitant **RIATEM** therapy should not be necessary; however dosing of the two medicines should be separated by 2,5 hours to avoid formulation incompatibility.

Digoxin:

Co-administration of the ritonavir component of **RIATEM** and digoxin may result in significantly increased digoxin levels. Caution should be exercised when co-administering **RIATEM** with digoxin, with appropriate monitoring of serum digoxin levels.

Efavirenz:

Co-administration of the ritonavir component of **RIATEM** with efavirenz may increase the steady state AUC of efavirenz, with an associated increase in the AUC of the ritonavir component of **RIATEM.**

Fluticasone propionate:

Concomitant use of the ritonavir component of **RIATEM** and fluticasone propionate may increase concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Fusidic acid:

Co-administration of the ritonavir component of **RIATEM** with fusidic acid may significantly increase fusidic acid and ritonavir concentrations in plasma.

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

Patients on **RIATEM** should not concomitantly use products containing St. John's Wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of **RIATEM**. This effect may be due to induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Indinavir:

The ritonavir component of **RIATEM** inhibits the CYP34A-mediated metabolism of indinavir and may increase the indinavir AUC, C_{max} and C_{min} resulting in increased indinavir serum concentrations. Safety of co-administration has not been established.

The risk of nephrolithiasis may be increased when higher doses of indinavir are co-administered with **RIATEM**. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole:

Concomitant administration of the ritonavir component of **RIATEM** with ketoconazole may result in an increase of mean ketoconazole AUC, half-life and C_{max}. Mean AUC and C_{max} of ritonavir also increases.

Methadone:

Co-administration of the ritonavir component of **RIATEM** with methadone may decrease methadone concentrations. A dosage increase of methadone may be considered.

Nelfinavir:

Interactions between the ritonavir component of **RIATEM** and nelfinavir are likely to involve both cytochrome P450 inhibition and induction. Concurrent administration of the ritonavir component of **RIATEM** may significantly increase the concentration (AUC) of M8 (the major active metabolite of nelfinavir).

Oral Contraceptive or Patch Contraceptive:

Concomitant administration of the ritonavir component of **RIATEM** and a fixed-combination oral contraceptive may result in reductions of the ethinyl estradiol mean C_{max} and AUC. Increased doses of oral contraceptives or patch contraceptives containing estradiol should be used, or alternate methods of contraception, should be considered. Co-administration of **RIATEM** with other hormonal contraceptives or oral contraceptives containing progestogens has not been studied, and therefore should be avoided. An alternate reliable method of contraception is recommended.

Rifabutin:

The concomitant administration of the ritonavir component of **RIATEM** and rifabutin may result in an increase in the AUC of rifabutin and its active metabolite 25-0-deacetyl rifabutin. 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:

The ritonavir component of **RIATEM** may extensively inhibit the metabolism of saquinavir, resulting in greatly increased saquinavir plasma concentrations. When used in combination therapy for a prolonged period of time and in big doses, there exists the possibility of an increase in adverse effects (see **WARNNGS AND SPECIAL PRECAUTIONS**).

Sildenafil:

Co-administration of the ritonavir component of **RIATEM** with sildenafil may 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. Caution should be exercised when prescribing sildenafil in patients receiving **RIATEM.**

Sulfamethoxazole/trimethoprim:

The concomitant administration of the ritonavir component of **RIATEM** and sulfamethoxazole/trimethoprim may result in a reduction of the sulfamethoxazole AUC and an increase of the trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant therapy with the ritonavir component should not be necessary.

Tadalafil:

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

Theophylline:

The concomitant administration of the ritonavir component of **RIATEM** and theophylline, may result in a decrease in the AUC of theophylline. An increased dosage of theophylline may be required.

Tobacco:

Tobacco use may be associated with an 18 % decrease in the AUC of the ritonavir component of **RIATEM**.

Trazodone:

Concomitant use of the ritonavir component of **RIATEM** and trazodone may increase concentrations of Trazodone. Adverse events of nausea, dizziness, hypotension and syncope may occur. If trazodone is used with a CYP3A4 inhibitor such as **RIATEM**, 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 the ritonavir component of **RIATEM** with voriconazole, may decrease voriconazole steady-state AUC by an average of 82 %. Co-administration of these medicines is therefore not recommended (see **CONTRAINDICATIONS**).

Warfarin:

Co-administration with the ritonavir component of **RIATEM** may induce the anticoagulant metabolism, resulting in decreased concentrations of warfarin.

Zidovudine:

The concomitant administration of the ritonavir component of **RIATEM** and zidovudine (AZT) may result in a reduction of the zidovudine C_{max} and AUC. In contrast, there may be little if any effect on the pharmacokinetics of the ritonavir component of **RIATEM.** Dose alteration of AZT during concomitant **RIATEM** therapy should not be necessary.

HUMAN REPRODUCTION

RIATEM:

- Is contraindicated for use during pregnancy and lactation, since the safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**).
- It is not known whether **RIATEM** is secreted in human milk.
- Because of both the potential for HIV transmission and the potential for serious adverse reactions in breastfed infants, mothers should be instructed not to breastfeed if they are taking **RIATEM.**
- It is not known whether **RIATEM** given to mothers will exacerbate physiologic hyperbilirubinaemia and lead to kernicterus in neonates and young infants

DOSAGE AND DIRECTIONS FOR USE

RIATEM:

- Each tablet must be taken with food. Atazanavir absorption is sensitive to food. Bioavailability of atazanavir sulphate (with or without the ritonavir boosted regimen) is enhanced if given with food and pharmacokinetic variability is reduced (see **Pharmacokinetics-**atazanavir sulphate-Absorption).
- The recommended dose is one tablet daily.
- Is recommended for treatment-naive or treatment-experienced patients with prior virologic failure.

Concomitant therapy with RIATEM:

Efavirenz:

See professional information Efavirenz

Tenofovir:

See professional information Tenofovir

Didanosine:

See professional information Didanosine

Dosage adjustments of RIATEM in Special Populations:

Renal impairment:

No dosage adjustment of **RIATEM** is recommended in patients with renal impairment (see **Pharmacokinetics-Special Populations**).

Hepatic impairment:

RIATEM should **not** be used in patients with moderate or severe hepatic impairment and should be used with caution in patients with mild hepatic impairment (see **Pharmacokinetics in special populations** and **CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS.**

SIDE-EFFECTS

SIDE-EFFECTS DUE TO THE ATAZANAVIR COMPONENT:

Immune system disorders:

Less frequent: Allergic reaction.

Metabolism and nutrition disorders:

***Less frequent*:** Anorexia, appetite increased, weight decreased, weight gain.

Psychiatric disorders:

***Less frequent*:** Anxiety, depression, sleep disorder.

Nervous system disorders:

Frequent: Dizziness, headache, insomnia, peripheral neurologic symptoms.

Less frequent: Abnormal dreams, amnesia, confusion and somnolence, abnormal gait.

Eye disorders:

***Frequent*:** Scleral icterus.

Cardiac disorders and vascular disorders:

Less frequent: Hypertension, syncope, oedema, palpitation, vasodilation.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea.

Gastrointestinal disorders:

Frequent: Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting.

Less frequent: Dry mouth, dysgeusia, flatulence, gastritis, pancreatitis, stomatitis aphthous, abdominal distension.

Hepato-biliary disorders:

Frequent: Jaundice.

Less frequent: Hepatitis, hepatosplenomegaly.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Less frequent: Lipodystrophy, alopecia, eczema, pruritus and urticaria, vesiculobullous rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema mutiforme.

Musculoskeletal, connective tissue and bone disorders:

***Less frequent*:** Arthralgia, muscle atrophy, myalgia, myopathy.

Renal and urinary disorders:

Less frequent: Haematuria, pollakiuria and proteinuria, kidney pain, nephrolithiasis (see **WARNINGS AND SPECIAL REACUTIONS**).

Reproductive system and breast disorders:

***Less frequent*:** Gynaecomastia.

General disorders and administration site conditions:

Frequent: Asthenia, fatigue.

Less frequent: Chest pain, fever, malaise.

SIDE-EFFECTS DUE TO THE RITONAVIR COMPONENT:

The most frequent clinical adverse events that may occur, other than asthenia, are gastrointestinal and neurological in nature. These events may include nausea, diarrhoea, vomiting, anorexia, abdominal pain, taste perversion and circumoral and peripheral paresthesias.

Infections and Infestations:

Frequent: Pharyngitis

Blood and the lymphatic systemic disorders:

Less frequent: Anaemia, ecchymosis, leukopenia, lymphadenopathy, Lymphocytosis and thrombocytopenia.

Immune system disorders:

Less frequent: Allergic reactions.

Endocrine disorders:

Less frequent: Diabetes melitus.

Metabolism and nutritional disorders:

Frequent: Anorexia, hyperlipemia, weight loss.

Less frequent: Avitaminosis, cachexia, dehydration, oedema, glycosuria, gout, hypercholesteremia, peripheral oedema and redistribution/accumulation of body fat (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Frequency unknown: Dehydration, usually associated with gastrointestinal symptoms, may sometimes result in hypotension, syncope or renal insufficiency. Syncope, orthostatic hypotension and renal insufficiency may also occur without known dehydration.

Psychiatric disorders:

Frequent: Anxiety and insomnia.

Less frequent: Agitation, confusion, depression, emotional lability, euphoria, hallucinations, decreased libido, nervousness, personality disorder and abnormal thinking.

Nervous system disorders:

Frequent: Circumoral paresthesia, headache, peripheral paresthesia, taste perversion, dizziness, hyperesthesia, paresthesia and somnolence.

Less frequent: Abnormal dreams, amnesia, aphasia, ataxia, convulsion, grand mal convulsion, incoordination, neuralgia, neuropathy, paralysis, parosmia, peripheral neuropathy, peripheral sensory neuropathy, taste loss, tremor and visual field defect.

Frequency unknown: Seizure.

Eye disorders:

Less frequent: Abnormal vision, amblyopia/blurred vision, blephartis, diplopia, eye pain, iritis, photophobia and uveitis.

Ear and labyrinth disorders:

Less frequent: Ear pain, hearing impairment, increased cerumen, tinnitus and vertigo.

Cardio-vascular disorders:

Less frequent: Palpitation, syncope, haemorrhage, hypotension, migraine, peripheral vascular disorder, postural hypotension, and tachycardia.

Frequency unknown: Myocardial infarction.

Respiratory, thoracic and mediastinal disorders:

Frequent: Increased cough.

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

Gastro intestinal disorders:

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

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

Hepato-biliary disorders:

Less frequent: Cholangitis, hepatitis, hepatomegaly and liver damage.

Skin and subcutaneous tissue disorders:

Frequent: Maculopapular rash, pruritus, rash and sweating.

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

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia.

Less frequent: Arthalgia, arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness, myositis, neck pain, neck rigidity, rhabdomyolysis and twitching.

Renal and urinary disorders:

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

Reproductive system and breast disorders:

Less frequent: Impotence and penis disorder.

Frequency unknown: Menorrhagia.

General disorders and administrative site conditions:

Frequent: Asthenia, fever and pain.

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

Investigations:

Frequent: Abnormal liver function test.

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

Injury and poisoning:

Less frequent: Accidental injury and hypothermia.

Surgical and medical procedures:

Frequent: Vasodilation.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT

RIATEM:

Symptoms of overdose:

- Human experience of acute overdose with **RIATEM** is limited.
- At high doses that lead to high medicine exposures, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations, may occur.
- High doses of the ritonavir component may cause paresthesias which may resolve after the dose is decreased.
- An overdose with the ritonavir component may cause renal failure with eosinophilia.

Management of overdose:

- There is no specific antidote for overdose with **RIATEM**.
- Treatment should consist of general supportive measures, including monitoring of vital signs,

electrocardiogram and observations of the patient's clinical status.

- Administration of activated charcoal may also be used to aid removal of unabsorbed medicine.
- Since **RIATEM** is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

IDENTIFICATION

Creamish yellow coloured, modified capsule shaped film-coated tablet debossed with “EM” on one side and “149” on the other side.

PRESENTATION

RIATEM:

Pack size 28’s and 30’s: Tablets are packed in a 120-cc white opaque HDPE container sealed with a 38 mm white opaque child-resistant closure with an induction seal and two silica gel pouches inside the container. The HDPE container is packed in an outer carton.

Pack size 84’s and 90’s: Tablets are packed in a 250-cc white opaque HDPE container sealed with 53 mm white opaque closure with an induction seal and two silica gel pouches inside the container. The HDPE container is packed in an outer carton.

Pack size 168’s and 180’s: Tablets are packed in a 500-cc white opaque HDPE container sealed with 53 mm white opaque closure with an induction seal and two silica gel pouches inside the container. The HDPE container is packed in an outer carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from moisture. Keep the bottles tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

48/20.2.8/1248

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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