PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

REYATAZ 150 mg CAPSULES

REYATAZ 200 mg CAPSULES

COMPOSITION:

Each capsule contains the equivalent of 150 mg and 200 mg of atazanavir as atazanavir sulphate. Contains sugar (lactose monohydrate).

Inactive ingredients: lactose monohydrate, crospovidone, magnesium stearate, gelatine, FD&C Blue # 2 and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral Agents.

REYATAZ (atazanavir sulphate) is an azapeptide inhibitor of HIV-1 protease.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

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

Pharmacokinetic properties

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

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

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

Atazanavir is 86 % bound to human serum proteins.

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

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

Microbiology

Resistance in vitro:

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

Resistance in vivo:

Distinct resistance patterns appeared in atazanavir-containing regimens depending on whether patients had previously received protease inhibitor therapy and whether their

study treatment utilised unboosted atazanavir as the only protease inhibitor or, atazanavir plus ritonavir.

Treatment-naïve patients

Atazanavir 400 mg with ritonavir: The I50L substitution, sometimes in combination with an A71V change, is the signature resistance change for atazanavir. Of the 25 resistant isolates emerging in treatment-naïve patient studies, 23 had an I50L substitution emerge on atazanavir therapy. There was no evidence of cross-resistance between atazanavir and amprenavir. Phenotypic analysis of the I50L-containing isolates showed atazanavir-specific resistance, which coincided with increased susceptibility to other protease inhibitors.

Atazanavir 300 mg with 100 mg ritonavir: In a study of treatment-naïve patients comparing the efficacy of atazanavir plus ritonavir 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.

INDICATIONS:

REYATAZ is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in children from the age of 6 years and in adult patients. The efficacy of REYATAZ has been demonstrated in antiretroviral-naïve and treatment-experienced patients.

CONTRAINDICATIONS:

REYATAZ is contraindicated in patients with known hypersensitivity to any of its ingredients, including atazanavir.

(See **DOSAGE AND DIRECTIONS FOR USE: *Hepatic impairment*; WARNINGS AND SPECIAL PRECAUTIONS: Hepatic impairment and toxicity; INTERACTIONS: Medicines that should not be administered with REYATAZ**).

REYATAZ is contraindicated when co-administered with medicines that are highly dependent on CYP3A4 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see **INTERACTIONS**).

REYATAZ is contraindicated in mothers breastfeeding their infants (see **PREGNANCY AND LACTATION**).

Voriconazole should not be administered to patients receiving REYATAZ and ritonavir (see **INTERACTIONS**).

Table 1: Medicines that are Contraindicated with REYATAZ

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

GI Motility Medicine: cisapride	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum)*	Patients taking REYATAZ should not use products containing St. John's wort because co-administration may be expected to reduce plasma concentrations of atazanavir. This may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	There may be potential for serious reactions such as myopathy including rhabdomyolysis. (See **INTERACTIONS: Other medicines,** HMG-CoA Reductase Inhibitors).
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Sedative Hypnotics: Orally administered midazolam, triazolam	Potential for increased concentrations of the sedative hypnotic and increased risk of prolonged sedation or respiratory depression.
PDE5 inhibitor: sildenafil	A safe and effective dose in combination with REYATAZ 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	REYATAZ inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.
Protease Inhibitor: indinavir	REYATAZ and indinavir are associated with hyperbilirubinaemia. Co-administration of REYATAZ and indinavir is not recommended. (See **SIDE EFFECTS**).

WARNINGS AND SPECIAL PRECAUTIONS:

Lipodystrophy and metabolic abnormalities:

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

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

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.

Immune Reconstitution Inflammatory Syndrome (IRIS):

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART), including REYATAZ. Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are *Mycobacterium avium* infection, cytomegalovirus retinitis, *Pneumocystis jiroveci* pneumonia, tuberculosis and cryptococcal meningitis.

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

Osteonecrosis:

Although the 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 REYATAZ 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 REYATAZ, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

PR Interval:

REYATAZ has the potential to prolong the PR interval of the electrocardiogram in some patients. REYATAZ should be used with caution in patients with pre-existing conduction system disease. Caution should be used when co-administering REYATAZ with medicines known to induce PR interval prolongation.

Rash:

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with REYATAZ. In most patients, rash resolves within 2 weeks while continuing REYATAZ therapy. REYATAZ 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 receiving REYATAZ.

Hepatic impairment and toxicity:

REYATAZ is principally metabolised by the liver; caution should be exercised when administering REYATAZ to patients with hepatic impairment because REYATAZ concentrations may be increased. (See **DOSAGE & DIRECTIONS FOR USE:** ***Hepatic Impairment***). Patients with underlying hepatitis B or C viral infections or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations.

Nephrolithiasis:

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

Hyperbilirubinaemia:

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ 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 REYATAZ may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of REYATAZ is not recommended since long-term efficacy of reduced doses has not been established.

Effects on ability to drive and use machines: There have been reports of adverse nervous system side effects that may influence the patient's ability to drive or use machines (see **SIDE EFFECTS).**

Lactose: REYATAZ contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take REYATAZ.

INTERACTIONS:

REYATAZ is metabolised in the liver by the cytochrome P450 enzyme system, and is an inhibitor of CYP3A4 (cytochrome P450 3A4). Co-administration of REYATAZ and medicines primarily metabolised by CYP3A4 (calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, and PDE5 inhibitors) may result in increased plasma concentrations of the other medicine that could increase or prolong both its therapeutic and adverse effects.

Co-administration of REYATAZ and medicines that induce CYP3A4, such as rifampicin, may decrease REYATAZ plasma concentrations and reduce its therapeutic effect. Co-administration of REYATAZ and medicines that inhibit CYP3A4 may increase REYATAZ plasma concentrations. The magnitude of CYP3A4-mediated interactions (effect on REYATAZ or effect on co-administered medicine) may change when REYATAZ is co-administered with ritonavir, a potent CYP3A4 inhibitor. The prescribing information for ritonavir should be consulted for information on interactions with ritonavir.

Caution should be used when co-administering REYATAZ with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, verapamil). (See **SIDE EFFECTS**).

Inhaled beta-2 agonists: salmeterol:

Concomitant use of salmeterol and REYATAZ may result in increased cardiovascular adverse events associated with salmeterol. Co-administration of salmeterol and REYATAZ is not recommended.

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

HIV Antiviral medicines

Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Didanosine: Co-administration of didanosine buffered tablets and REYATAZ markedly decreased exposure to REYATAZ (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Co-administration with REYATAZ did not alter exposure to didanosine. Administration of the enteric-coated formulation of didanosine with REYATAZ or atazanavir/ritonavir and a light meal decreased exposure to didanosine. (See **DOSAGE AND DIRECTIONS FOR USE** - ***Concomitant Therapy***).

Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Tenofovir: Exposure to REYATAZ is decreased when tenofovir is co-administered with REYATAZ. (See **DOSAGE AND DIRECTIONS FOR USE** - ***Concomitant Therapy***). REYATAZ increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving REYATAZ and tenofovir should be monitored for tenofovir-associated adverse events.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Efavirenz: Exposure to REYATAZ is decreased when efavirenz is co-administered with REYATAZ. Co-administration of REYATAZ with efavirenz is not recommended.

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

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

Protease Inhibitors:

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

Ritonavir: Exposure to REYATAZ is increased when ritonavir is co-administered with REYATAZ. (See **DOSAGE AND DIRECTIONS FOR USE**).

Other protease inhibitors:

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

Other medicines

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

Antidysrhythmics:

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

monitoring is recommended when available. Quinidine is contraindicated when REYATAZ is co-administered with ritonavir.

Anticoagulants:

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

Antidepressants:

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

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

Antifungals:

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

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

Antimycobacterials:

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

Calcium Channel Blockers:

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

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

Erectile Dysfunction medicines:

Phosphodiesterase (PDE5) inhibitors: Co-administration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in PDE5 inhibitor-associated adverse events. Use with caution and monitor for adverse events. Use of sildenafil for the treatment of pulmonary arterial hypertension is contraindicated with REYATAZ. (See **CONTRAINDICATIONS**.)

Proton-pump Inhibitors: REYATAZ co-administered with proton pump inhibitors results in a substantial decrease in atazanavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg or REYATAZ 300 mg/ritonavir 100 mg once daily was administered with omeprazole 20 mg once daily. An

increased dose of REYATAZ 400 mg/ritonavir 100 mg, may be administered with omeprazole at a maximum dose of 20 mg once daily (or comparable dose of an alternative proton-pump inhibitor) to HIV infected patients without suspected or documented evidence of decreased susceptibility to atazanavir. Doses of omeprazole exceeding 20 mg daily (or comparable dose of an alternative proton-pump inhibitor) are not recommended.

H_2-Receptor Antagonists:

Plasma concentrations of atazanavir were substantially decreased when REYATAZ 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. In treatment-naïve patients, REYATAZ 400 mg may be administered once daily with food 2 hours before and at least 10 hours after the administration of an H_2-receptor antagonist. However, a single dose of the H_2-receptor antagonist should not exceed a dose comparable to famotidine 20 mg and the total daily dose should not exceed a dose comparable to famotidine 40 mg. Alternatively, REYATAZ 300 mg with ritonavir 100 mg once daily with food may be administered simultaneously with, or at least 2 hours before and at least 10 hours after a dose of an H_2-receptor antagonist.

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

In treatment-experienced patients taking REYATAZ/ritonavir and tenofovir with an H_2-receptor antagonist, REYATAZ 400 mg with ritonavir 100 mg once daily should be administered.

HMG-CoA Reductase Inhibitors:

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

Immunosuppressants:

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

Inhaled/nasal corticosteroids (interaction with ritonavir):

In healthy volunteers, ritonavir significantly increased plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of REYATAZ/ritonavir with fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir was co-administered with inhaled or intranasally administered fluticasone propionate. These effects could also occur with other corticosteroids metabolised via the cytochrome P450 3A pathway, e.g. budesonide. Therefore, concomitant use of REYATAZ/ritonavir and fluticasone propionate or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential

benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use of fluticasone propionate and REYATAZ (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with Caution. Consider alternatives to fluticasone propionate, particularly for long-term use.

Macrolide Antibiotics:

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

Benzodiazepines:

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

Opioids:

Buprenorphine: Concentrations of buprenorphine and norbuprenorphine were increased when buprenorphine was co-administered with REYATAZ, with or without ritonavir, due to CYP3A4 and UGT1A1 inhibition. Co-administration of REYATAZ plus ritonavir with

buprenorphine warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered. There was no significant effect on atazanavir plasma concentration when REYATAZ plus ritonavir were co-administered with buprenorphine. Co-administration of buprenorphine and REYATAZ without ritonavir may substantially decrease atazanavir plasma concentrations. REYATAZ without ritonavir should not be co-administered with buprenorphine.

Oral Contraceptives:

Ethinylestradiol and norethindrone:

Mean concentrations of ethinylestradiol and norethindrone are increased when they are co-administered with REYATAZ. 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 REYATAZ is taken with ritonavir. Administration of REYATAZ plus ritonavir with ethinylestradiol and norgestimate decreases the mean concentration of ethinylestradiol by 20 % and increases the mean concentration of 17-deacetyl norgestimate by 68 %, the active metabolite of norgestimate. If an oral contraceptive is administered with REYATAZ plus ritonavir, it is recommended that the oral contraceptive contain at least 30 µg of ethinylestradiol. If REYATAZ is administered without ritonavir, the oral contraceptive should contain no more than 30 µg of ethinylestradiol. Use with caution as the effect of increases in concentration of the progestational medicines are unknown and could increase the risk of acne, dyslipidaemia, and insulin resistance.

Co-administration of REYATAZ or REYATAZ/ritonavir with other hormonal contraceptives (e.g., contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norethindrone or norgestimate, or less

than 25 µg of ethinyl oestradiol have not been studied; therefore alternative methods of contraception are recommended.

Effect on other Cytochrome P450 (CYP) enzymes:

Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when REYATAZ without ritonavir is co-administered with medicines highly dependent on CYP2C8 with narrow therapeutic indices.

PREGNANCY AND LACTATION:

Safe use during pregnancy has not been established.

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

Dosing during Pregnancy and the Postpartum Period

- REYATAZ should not be administered without ritonavir.
- For pregnant patients, no dose adjustment is required for REYATAZ with the following exceptions:
    - For treatment-experienced pregnant women during the second or third trimester, when REYATAZ is co-administered with either an H_2-receptor antagonist *or* tenofovir, REYATAZ 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a REYATAZ dose for use with *both* an H_2-receptor antagonist ***and*** tenofovir in treatment-experienced women.

- No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposure could be higher during the first 2 months after delivery.

It is not known whether REYATAZ is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in breast-fed infants, mothers receiving REYATAZ should be instructed not to breastfeed their infants. (See **CONTRAINDICATIONS**.)

DOSAGE AND DIRECTIONS FOR USE:

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

Recommended adult dosage

The recommended dose of Reyataz is:

Treatment-Naïve Patients:

- 300 mg once daily with ritonavir 100 mg once daily taken with food.
- 400 mg once daily with food.

Treatment-Experienced Patients:

- 300 mg once daily with ritonavir 100 mg once daily taken with food.

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

Recommended paediatric and adolescent dosage

REYATAZ Capsules (paediatric patients at least 6 years of age)

The dosage of REYATAZ for paediatric patients (6 to 18 years of age) should be calculated based on body weight and should not exceed the recommended adult dose.

Paediatric Dose for REYATAZ Capsules with ritonavir

(6 to less than 18 years of age)[a]

Body weight (kg)	**REYATAZ dose (mg)**	**ritonavir dose**[b] **(mg)**
15 to less than 20	150	100[c]
20 to less than 40	200	100
At least 40	300	100

[a] The REYATAZ and ritonavir dose should be taken once daily with food.

[b] Ritonavir capsules, tablets or oral solution

[c] Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets.

There are no dosing recommendations for REYATAZ in paediatric patients less than 6 years of age. REYATAZ should not be administered to paediatric patients below the age of 3 months due to risk of kernicterus.

For treatment-naïve patients at least 13 years of age and at least 40 kg, who are unable to tolerate ritonavir, the recommended dose is REYATAZ 400 mg (without ritonavir) once daily with food.

Concomitant Therapy:

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

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

Renal Impairment:

In patients with renal impairment, including those with severe renal impairment who are not managed by haemodialysis, no dosage adjustment is required for REYATAZ. For treatment-naïve patients managed with haemodialysis, administration of REYATAZ 300 mg with ritonavir 100 mg is recommended. REYATAZ should not be administered to HIV-treatment-experienced patients with severe renal impairment managed with haemodialysis.

Hepatic Impairment:

REYATAZ should be used with caution in patients with mild to moderate hepatic impairment. A dose reduction to 300 mg once daily should be considered for patients with moderate hepatic impairment. REYATAZ should not be used in patients with severe hepatic impairment. REYATAZ in combination with ritonavir has not been studied in subjects with hepatic impairment and should be used with caution in patients with mild hepatic impairment. REYATAZ with ritonavir is not recommended for patients with moderate-severe impairment. (See **SIDE EFFECTS**).

SIDE EFFECTS:

REYATAZ has been evaluated for safety and tolerability in combination therapy with other antiretroviral medicines in controlled clinical trials in adult patients who received REYATAZ 400 mg once daily or REYATAZ 300 mg once daily plus ritonavir 100 mg once daily.

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

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

Frequency is defined as very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000) or very rare (< 1/10000).

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

Cardiac disorders	Uncommon:	syncope
	Rare:	oedema, palpitation
Nervous system disorders	Common:	headache

	Uncommon:	peripheral neurologic symptoms, amnesia, somnolence, dizziness, dysgeusia
Eye disorders	Common:	scleral icterus
Respiratory, thoracic and mediastinal disorders	Uncommon:	dyspnoea
Gastrointestinal disorders	Common:	abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
	Uncommon:	dry mouth, flatulence, gastritis, pancreatitis, stomatitis aphthous, abdominal distension
Renal and urinary disorders	Uncommon:	haematuria, pollakiuria, proteinuria, nephrolithiasis, interstitial nephritis
	Rare:	kidney pain
Skin and subcutaneous tissue disorders	Common:	rash
	Uncommon:	alopecia, pruritus, urticaria, DRESS syndrome, angioedema
	Rare:	vasodilation, vesiculobullous rash, eczema, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Uncommon:	arthralgia, muscle atrophy, myalgia
	Rare:	myopathy

Metabolism and nutrition disorders	Uncommon:	anorexia, increased appetite, decreased weight, weight gain
Vascular disorders	Uncommon:	hypertension
General disorders and administration site conditions	Common: Uncommon:	asthenia, fatigue chest pain, fever, malaise, gait disturbance
Immune system disorders	Uncommon:	allergic reaction
Hepatobiliary disorders	Common: Uncommon: Rare:	jaundice hepatitis hepatosplenomegaly
Reproductive system and breast disorders	Uncommon:	gynaecomastia
Psychiatric disorders	Uncommon:	anxiety, depression, sleep disorder, insomnia, abnormal dream, disorientation

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 REYATAZ and comparator regimens. No differences in frequency of bilirubin elevations were observed.

Paediatric patients:

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

The most common Grade 2 – 4 adverse events (≥ 5 %, regardless of causality) reported in paediatric patients were cough, fever, jaundice/scleral icterus, rash, vomiting,

diarrhoea, headache, peripheral oedema, extremity pain, nasal congestion, oropharyngeal pain, wheezing and rhinorrhea. Asymptomatic second-degree atrioventricular block was reported in < 2 % of patients.

Laboratory findings:

Adult Patients

The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect (unconjugated) bilirubin (87 % Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37 % (6 % Grade 4).

Other marked clinical laboratory abnormalities (Grade 3 or 4) reported in $\geq$ 2 % of patients receiving regimens containing REYATAZ and one or more NRTIs included: elevated creatine kinase (CK) (7 %), elevated ALT/SGPT (5 %), low neutrophils (5 %), elevated AST/SGOT (3 %), and elevated lipase (3 %).

In clinical studies, the observed magnitude of dyslipidaemia was less with REYATAZ than with comparators.

Paediatric patients:

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

Post-marketing experience:

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

Cardiac disorders and vascular disorders: Second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes. (See **WARNINGS AND SPECIAL PRECAUTIONS**).

Metabolism and nutrition disorders: Hyperglycaemia, diabetes mellitus. (See **WARNINGS AND SPECIAL PRECAUTIONS**).

Renal and urinary disorders: Nephrolithiasis.

Hepatobiliary disorders: Cholelithiasis, cholecystitis, cholestasis.

KNOWN SYMPTOMS OF OVERDOSAGE & PARTICULARS OF ITS TREATMENT:

Human experience of acute overdose with REYATAZ is limited. Single doses up to 1200 mg have been taken by healthy volunteers without symptomatic untoward effects. A single self-administered overdose of 29,2 g of REYATAZ in an HIV-infected patient (73 times the 400 mg recommended dose) was associated with asymptomatic bifascicular block and PR interval prolongation. These events resolved spontaneously. At high doses that lead to high medicine exposure, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations, may be observed.

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

IDENTIFICATION:

REYATAZ 150 mg CAPSULES: Size #1, two-piece, blue opaque cap and powder blue opaque body, hard gelatin capsule printed in white with “BMS”, “150 mg” and in blue with “3624”. Contents: White to light yellow granules which may appear as powder.

REYATAZ 200 mg CAPSULES: Size #0, two-piece, blue opaque cap and blue opaque body, hard gelatin capsule printed in white with “BMS”, “200 mg” and “3631”. Contents: White to light yellow granules which may appear as powder.

PRESENTATION:

REYATAZ Capsules are packed in white high-density polyethylene (HDPE) bottles with child resistant, white closure with an aluminium induction seal.
Each bottle will contain 60 capsules of 150 mg or 200 mg strength capsules.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from moisture. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

REYATAZ 150 mg CAPSULES: A39/20.2.8/0088

REYATAZ 200 mg CAPSULES: A39/20.2.8/0089

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

Equity Pharmaceuticals (Pty) Ltd*

100 Sovereign Drive

Route 21 Corporate Park

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Pretoria

DATE OF PUBLICATION OF THE PACKAGE INSERT:

25 November 2005

25 November 2016

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