APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

ZOROVIR 150 (capsule)

ZOROVIR 200 (capsule)

ZOROVIR 300 (capsule)

COMPOSITION:

ZOROVIR 150:

Each hard gelatin capsule contains atazanavir sulfate equivalent to atazanavir 150 mg. Contains sugar (lactose monohydrate).

ZOROVIR 200:

Each hard gelatin capsule contains atazanavir sulfate equivalent to atazanavir 200 mg. Contains sugar (lactose monohydrate).

ZOROVIR 300:

Each hard gelatin capsule contains atazanavir sulfate equivalent to atazanavir 300 mg. Contains sugar (lactose monohydrate).

The other ingredients of **ZOROVIR CAPSULES** are crospovidone, lactose monohydrate and magnesium stearate.

ZOROVIR 150: The capsule shell contains FD&C blue 2 (C.I. No: 73015), gelatin and titanium dioxide (C.I. No: 77891).

ZOROVIR 150: The black ink contains potassium hydroxide, propylene glycol, shellac, strong ammonia solution and titanium dioxide (C.I. No: 77891).

ZOROVIR 200: The capsule shell contains FD&C blue 2 (C.I. No: 73015), gelatin and titanium dioxide (C.I. No: 77891).

ZOROVIR 200: The black ink contains potassium hydroxide, propylene glycol, shellac, strong ammonia solution and titanium dioxide (C.I. No: 77891).

ZOROVIR 300: The capsule shell contains FD&C blue 2 (C.I. No: 73015), gelatin, iron oxide

black (C.I. No: 77499), iron oxide red (C.I. No: 77491), iron oxide yellow (C.I. No: 77492) and titanium dioxide (C.I. No: 77891).

ZOROVIR 300: The black ink contains potassium hydroxide, propylene glycol, shellac, strong ammonia solution and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral Agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Atazanavir is a peptide protease inhibitor that is active against both HIV-1 and HIV-2. **ZOROVIR** (atazanavir sulphate) is an azapeptide inhibitor of HIV-1 protease.

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 atazanavir as the only protease inhibitor or atazanavir plus saquinavir. Of the 23 resistant isolates emerging in treatment-naïve patient studies, all had a 150 L substitution emerge on atazanavir therapy. Phenotypic analysis of the 150 L-containing isolates showed atazanavir-specific resistance, which coincided with increased susceptibility to other protease inhibitors. In contrast ~ 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 150 L substitution, instead displaying decreased susceptibility to multiple protease inhibitors, which coincided with the accumulation of several additional amino acid substitutions, including 184V.

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

Pharmacokinetic properties

No substantial differences were reported between the pharmacokinetics of healthy adult

volunteers and in HIV-infected patients.

Absorption is increased by food and it is recommended that atazanavir be administered with a meal.

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 is 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.

INDICATIONS:

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

CONTRA-INDICATIONS:

ZOROVIR is contraindicated in patients with known hypersensitivity to atazanavir and to any of the other ingredients of **ZOROVIR**. Patients with severe hepatic impairment.

ZOROVIR is contraindicated in patients taking:

- Ergot Derivatives
- Antineoplatsic Medicines
- HMG- CoA Reductase Inhibitors
- Neuroleptic Medicines
- Protease Inhibitors
- Sedative Hypnotics
- Herbal products which contain St. John’s wort

- Antimycobacterial Medicines
- Calcium Channel Blockers

WARNINGS AND SPECIAL PRECAUTIONS:

Efficacy

Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥ 4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit.

Diabetes mellitus/Hyperglycaemia: New-onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported in HIV-infected patients receiving protease inhibitor therapy such as **ZOROVIR**. In some cases, diabetic ketoacidosis has been reported.

Patients should be advised that current antiretroviral therapy including **ZOROVIR** has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

Co-administration of **ZOROVIR** with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of **ZOROVIR** (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. Only when **ZOROVIR** with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close monitoring is warranted (see Interaction with other Medicinal Products below).

Patients with co-existing conditions

Hepatic impairment: Atazanavir is primarily hepatically metabolised and increased plasma concentrations were reported in patients with hepatic impairment. The safety and efficacy of **ZOROVIR** has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are

at an increased risk for severe and potentially fatal hepatic adverse reactions.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal impairment: No dosage adjustment is needed in patients with renal impairment. However, **ZOROVIR** with ritonavir is not recommended in patients undergoing haemodialysis.

QT prolongation/PR interval: Dose related asymptomatic prolongations in PR interval with **ZOROVIR** have been reported. Caution should be used with medicines known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), **ZOROVIR** should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing **ZOROVIR** in association with medicines which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances).

Haemophiliac patients: There have been observations of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

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.

Hyperbilirubinaemia: Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving

ZOROVIR. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving **ZOROVIR** should be evaluated for alternative aetiologies. Alternative antiretroviral therapy to **ZOROVIR** may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of **ZOROVIR** is not recommended because it may result in a loss of therapeutic effect and development of resistance.

Indinavir is also associated with indirect (unconjugated hyperbilirubinaemia due to inhibition of UGT. Combinations of **ZOROVIR** and indinavir have not been studied and co-administration of these medicines is not recommended.

Nephrolithiasis: Nephrolithiasis has been reported in patients receiving **ZOROVIR**. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered.

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

Appropriate treatment of the opportunistic disease should be instituted or continued and CART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

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

Osteonecrosis: Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass

index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections: Patients receiving **ZOROVIR** 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.

Rash and associated syndromes: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with **ZOROVIR**.

Stevens-Johnson syndrome (SJS), erythema multiforme, toxic skin eruptions and medicine rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in patients receiving **ZOROVIR**. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. **ZOROVIR** should be discontinued if severe rash develops.

The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of **ZOROVIR**, **ZOROVIR** may not be restarted.

Interactions with other medicinal products

If the co-administration of **ZOROVIR** with an NNRTI is required, an increase in the dose of both **ZOROVIR** and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close monitoring.

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

Co-administration of **ZOROVIR** with proton pump inhibitors is not recommended. If the combination of **ZOROVIR** with a proton pump inhibitor is judged unavoidable, close

monitoring is recommended in combination with an increase in the dose of **ZOROVIR** to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

Co-administration of **ZOROVIR**/ritonavir with other hormonal contraceptives or oral contraceptives containing progestogens other than norgestimate has not been studied, and therefore should be avoided.

Lactose

ZOROVIR contains lactose and should not be given to patients with rare hereditary problems or a history of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Paediatric population

Safety

Very little information is available in children 4 – 18 years.

Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients. Caution should be used with medicines known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), **ZOROVIR** should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia).

Ability to drive and use machines:

ZOROVIR may cause dizziness. Caution should be exercised while driving or operating machinery until you know how **ZOROVIR** affects the patient.

INTERACTIONS:

ZOROVIR is metabolised in the liver by the cytochrome P450 enzyme system, and is an inhibitor of CYP3A4 (cytochrome P450 3A4). Co-administration of **ZOROVIR** 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 **ZOROVIR** and medicines that induce CYP3A4, such as rifampicin, may decrease **ZOROVIR** plasma concentrations and reduce its therapeutic effect. Co-administration of **ZOROVIR** and medicines that inhibit CYP3A4 may increase **ZOROVIR** plasma concentrations. The magnitude of CYP3A4-mediated medicine interactions (effect on **ZOROVIR** or effect on coadministered medicine) may change when **ZOROVIR** is coadministered with ritonavir, a potent CYP3A4 inhibitor. The prescribing information for ritonavir should be consulted for information on medicine interactions with ritonavir. When ritonavir-boosted atazanavir is given, the interaction profile for titonavir may predomniate because ritonavir is a more potent CYP3A4 inhibitor than **ZOROVIR**.

Caution should be used when coadministering **ZOROVIR** with medicines known to induce PR interval prolongation (e.g. atenolol, diltiazem, verapamil). (**See Warnings & Special Precautions**).

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

Medicines that should not be administered with ZOROVIR:

PDE5 inhibitors used for the treatment of erectile dysfunction: particular caution should be used when prescribing PDE5-inhibitors (sildenafil, tadalafil, or vardenafil) for the treatment of erectile dysfunction in patients receiving **ZOROVIR** with concomitant low-dose ritonavir. Co-administration of **ZOROVIR** with these medicinal products is expected to substantially increase their concentrations and may result in PDE5-associated adverse events such as hypotension, visual changes and priapism.

Antidysrhythmic medicines: Amiodarone, lidocaine (systemic), quinidine: Concentrations may be increased when co-administered with **ZOROVIR.** Caution is warranted and therapeutic concentration monitoring is recommended when available. *Quinidine:* **ZOROVIR/ritonavir:**

Contraindicated if **ZOROVIR** is coadministered with ritonavir due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

Antimycobacterial medicines: Rifampicin substantially decreases plasma concentrations of **ZOROVIR**, which may result in loss of therapeutic effect and development of resistance.

Antineoplastic medicines: Irinotecan: **ZOROVIR** inhibits UDP-glucuronosyltransferase (UGT) and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicity.

Calcium Channel Blockers: Bepridil: Potential for serious and/or life-threatening adverse events. Contraindicated if **ZOROVIR** is coadministered with ritonavir.

Ergot Derivatives: Dihydroergotamine, ergotamine, ergonovine, methylergonovine: Contraindicated due to potential for serious and/or life-threatening events such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.

GI Motility medicine: Cisapride: Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.

HMG-CoA Reductase Inhibitors: Lovastatin, simvastatin: There may be potential for serious reactions such as myopathy including rhabdomyolysis.

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

Protease Inhibitor: Indinavir: **ZOROVIR** and indinavir are associated with hyperbilirubinemia. Coadministration of **ZOROVIR** and indinavir is not recommended. (**See Warnings & Special Precautions).**

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

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

Herbal Product: St. John's wort (Hypericum perforatum): Patients taking **ZOROVIR** should not use products containing St. John's wort *(Hypericum perforatum)* because coadministration may be expected to reduce plasma concentrations of atazanavir. This may

result in loss of therapeutic effect and development of resistance.

HIV Antiviral Medicines

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Didanosine: Coadministration of didanosine buffered tablets and **ZOROVIR** marked by decreased exposure to **ZOROVIR** (presumably due to the increase in gastric pH caused by buffers in the didanosine tablets). Coadministration with **ZOROVIR** did not alter exposure to didanosine. Administration of the enteric-coated formulation of didanosine with **ZOROVIR** or atazanavir/ritonavir and a light meal decreased exposure to didanosine. **(See Dosage & Directions for use – Concomitant therapy.)**

Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Tenofovir: Exposure to **ZOROVIR** is decreased when tenofovir is coadministered with **ZOROVIR**. (**See Dosage & Directions: Concomitant therapy**). **ZOROVIR** increases tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving **ZOROVIR** and tenofovir should be monitored for tenofovir-associated adverse events.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Efavirenz: Exposure to **ZOROVIR** is decreased when efavirenz is coadministered with **ZOROVIR**. (**See Dosage & Direction: Concomitant therapy**).

Nevirapine: Nevirapine, an inducer of CYP3A4, is expected to decrease **ZOROVIR** exposure. In the absence of data, coadministration with **ZOROVIR** and ritonavir is not recommended.

Protease Inhibitors:

Saquinavir (soft gelatin capsules): Exposure to saquinavir is increased when it is coadministered with **ZOROVIR**. Appropriate dosing recommend- ations for this combination, with respect to efficacy and safety, have not been established.

Ritonavir: Exposure to **ZOROVIR** is increased when ritonavir is coadministered with **ZOROVIR. (See Dosage & directions for use).**

Other protease inhibitors:

Although not studied, the coadministration of **ZOROVIR** 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 medications: Reduced plasma concentrations of **ZOROVIR** may result if antacids, including buffered medications, are administered with **ZOROVIR. ZOROVIR** should be administered 2 hours before or 1 hour after these medicines.

Anticoagulants:

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

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

Antifungals:

High doses of ketocoazole and itraconazole (> 200 mg/day) should be used cautiously with **ZOROVIR** and ritonavir. Voriconazole should not be administered to patients receiving **ZOROVIR** and ritonavir.

Antimycobacterials:

Rifabutin: Exposure to rifabutin is increased when it is coadministered with **ZOROVIR.** A rifabutin dose reduction of up to 75 % (e.g. 150 mg every other day or 3 times per week) is recommended.

Calcium Channel Blockers:

Diltiazem: Exposure to diltiazem and a metabolite, desacetyl-diltiazem, is increased when diltiazem is coadministered with **ZOROVIR.** 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.

H_2-Receptor Antagonists:

Plasma concentrations of **ZOROVIR** are substantially decreased when **ZOROVIR** 400 mg once daily is administered simultaneously with famotidine 40 mg twice daily, which may result in loss of therapeutic effect and development of resistance. When coadministered with H_2-receptor antagonist, the recommended dose is **ZOROVIR** 300 mg with ritonavir 100 mg (all as a single daily dose with food) for all patients. Alternatively, for treatment-naïve patients, **ZOROVIR** 400 mg may be administered once daily with food 2 hours before and at least 10 hours after the administration of H_2-receptor antagonist. To minimise any reduction in **ZOROVIR** concentrations in patients receiving **ZOROVIR** 300 mg/ritonavir 100 mg and H_2-receptor antagonist, temporal separation may also be considered with this dosing regimen.

HMG-CoA Reductase Inhibitors:

Atorvastatin: Exposure to atorvastatin may be increased when it is coadministered with **ZOROVIR.** The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including **ZOROVIR**, are used in combination with atorvastatin. Caution should be exercised **(See Medicines that should not be administered with ZOROVIR: HMG-CoA Reductase Inhibitors).**

Immunosuppressants:

Ciclosporin, tacrolimus, sirolimus: Exposure to ciclosporin, tacrolimus and sirolimus may be increased when they are coadministered with **ZOROVIR.** Therapeutic concentation monitoring is recommended for immuno- suppressant medicineswhen coadministered with **ZOROVIR.**

Inhaled/nasal corticosteroids (interaction with ritonavir):

In healthy volunteers, ritonavir significantly increased plasma fluticasone propionate exposure, resulting in significantly decreased serum cortisol concentrations. Concomitant use of **ZOROVIR**/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 coadministered 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 **ZOROVIR**/ritonavir and fluticasone propionate or other glucocorticoids that are metabolised by CYP3A4 is not recommended. Concomitant use of fluticasone propionate and **ZOROVIR** (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 coadministered with **ZOROVIR**. Increased concentrations of clarithromycin may cause QTc prolongations; therefore, a dose reduction of clarithromycin by 50 % should be considered when it is coadministered with **ZOROVIR**.

Oral Contraceptives:

Ethinyl estradiol and norethindrone: Mean concentrations of ethinyl estradiol and norethindrone are increased when they are coadministered with **ZOROVIR**. 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 nonhormonal contraception should be considered when **ZOROVIR** is taken with ritonavir.

PREGNANCY AND LACTATION:

There are no adequate and well-controlled studies in pregnant women. **ZOROVIR** should not be used during pregnancy.

Hyperbilirubinaemia may occur frequently during treatment with **ZOROVIR**. It is not known whether **ZOROVIR** 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 **ZOROVIR** should be considered.

It is not known whether **ZOROVIR** 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 should be instructed not to breast-feed their infants if they are receiving **ZOROVIR**.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose of **ZOROVIR** is 400 mg once daily taken with food. When coadministered with ritonavir, it is recommended that **ZOROVIR** 300 mg once daily be taken with ritonavir 100 mg once daily with food.

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

Concomitant Therapy:

Efavirenz: In treatment-naive patients, it is recommended that **ZOROVIR** 300 mg and ritonavir 100 mg be taken with efavirenz 600 mg (all once daily). **ZOROVIR** without ritonavir should not be coadministered with efavirenz. Dosing recommendations for efavirenz and **ZOROVIR** in treatment-experienced patients with prior virologic failure have not been established.

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

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

Renal Impairment: In patients with renal impairment no dosage adjustment is recommended.

Hepatic Impairment: **ZOROVIR** 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. **ZOROVIR** should not be used in patients with severe hepatic impairment. **ZOROVIR** 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. **ZOROVIR** with ritonavir is not recommended for patients with moderate-severe impairment. **(See Contraindications, Warnings & Special Precautions: Hepatic Impairment).**

Paediatric Patients. The optimal dosing regimen for use of **ZOROVIR** in paediatric patients has not been established. **ZOROVIR** should not be administered to paediatric patients below the age of 3 months. **(See Pharmacokinetics: Paediatrics).**

SIDE-EFFECTS:

ZOROVIR may have side-effects. These are classified as follows:

Immune system disorders:

Less frequent: Hypersensitivity, allergic reactions

Metabolism and nutrition disorder:

Less frequent: Diabetes, hyperglycaemia, decreased weight, weight gain, anorexia, increased appetite.

Psychiatric disorders:

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

Nervous system disorders:

Frequent: Headache.

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

Eye disorders:

Frequent: Ocular icterus.

Cardiac disorders:

Less frequent: Torsades de pointes.

Rare: QTc prolongation, oedema, palpitation.

Vascular disorders:

Less frequent: Hypertension.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea.

Gastrointestinal disorders:

Frequent: Vomiting, diarrhoea, abdominal pain, nausea, dyspepsia.

Less frequent: Pancreatitis, gastritis, abdominal distension, stomatitis aphthous, flatulence, dry mouth, dysgeusia.

Hepatobiliary disorders:

Frequent: Jaundice.

Less frequent: Hepatitis, cholilithiasis, cholestasis, hepatosplenomegaly, cholesystitis.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Less frequent: Erythemia multiforme, toxic skin eruptions, medicine rash with oesinophilia and systemic symptoms (DRESS) syndrome, urticaria, alopecia, pruritus, Stevens-Johnson syndrome, vesiculobullous rash, eczema, vasodilaiton.

Musculoskeletal and connective tissue disorders:

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

Renal and urinary disorders:

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

Reproductive system and breast disorders:

Less frequent: Gynaecomastia.

General disorders and administration site conditions:

Frequent: Lipodystrophy syndrome, fatigue.

Less frequent: Chest pain, malaise, pyrexia, asthenia.

KNOWN SYMPTOMS OF OVERDOSAGE & PARTICULARS OF ITS TREATMENT:

Human experience of acute overdose with **ZOROVIR** is limited. Overdose in an HIV-infected patient was associated with asymptomatic bifascicular block and PR interval prolongation. At high doses that lead to high medicine exposures, jaundice, predominantly due to indirect (unconjugated) hyperbilirubinaemia (without associated liver function test changes) or PR interval prolongations, may occur.

Treatment of overdosage with **ZOROVIR** 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 **ZOROVIR** should be achieved by emesis of gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed atazanavir. There is no specific antidote for overdose with **ZOROVIR**. Since **ZOROVIR** is extensively metabolised by the liver and is highly protein bound, dialysis is

unlikely to be beneficial in significant removal of atazanavir.

IDENTIFICATION:

ZOROVIR 150:

Blue/Powder blue size '1' hard gelatin capsule filled with off-white to pale yellow granular powder and imprinted with '150 mg' on blue cap and 'T24' on Powder blue body with white edible ink.

ZOROVIR 200:

Blue/Blue size '0' hard gelatin capsule filled with off-white to pale yellow granular powder and imprinted with '200 mg' on blue cap and 'T25' on blue body with white edible ink

ZOROVIR 300:

Red/Blue size '00' hard gelatin capsule filled with off-white to pale yellow granular powder and imprinted with '300 mg' on red cap and 'T26' on blue body with white edible ink.

PRESENTATION:

ZOROVIR 150:

1) **Blister pack:**

   Capsules are packed in 25 micrometer polyamide/ 45 micron aluminium foil/ 60 micron PVC film as the forming material and 25 micron aluminium foil with 7 g/m^2 heat seal lacquer as the lidding material.

   Pack size: 60's - Each carton contains 6 blisters of 10 capsules each.

2) **HDPE Container Pack:**

   Capsules are packed in white opaque round 75 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene child resistant closure with wad having induction sealing liner.

   Pack size: 60's - One HDPE container contains 60 capsules.

ZOROVIR 200:

1) **Blister pack:**

   Capsules are packed in 25 micrometer polyamide/ 45 micron aluminium foil/ 60 micron PVC film as the forming material and 25 micron aluminium foil with 7 g/m^2 heat seal

lacquer as the lidding material.

Pack size: 60's - Each carton contains 6 blisters of 10 capsules each.

2) HDPE Container Pack:

Capsules are packed in white opaque round 120 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene child resistant closure with wad having induction sealing liner.

Pack size: 60's - One HDPE container contains 60 capsules.

ZOROVIR 300:

1) Blister pack:

Capsules are packed in 25 micrometer polyamide/ 45 micron aluminium foil/ 60 micron PVC film as the forming material and 25 micron aluminium foil with 7 g/m^2 heat seal lacquer as the lidding material.

Pack size: 30's - Each carton contains 3 blisters of 10 capsules each.

2) HDPE Container Pack:

Capsules are packed in white opaque round 75 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene child resistant closure with wad having induction sealing liner.

Pack size: 30's - One HDPE container contains 30 capsules.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from moisture.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

Keep all medicines out of the reach and sight of children.

REGISTRATION NUMBER:

To be allocated.

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

Aurobindo Pharma (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

To be allocated.