PROFESSIONAL INFORMATION FOR

LOPIMUNE 40/10 ORAL PELLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

LOPIMUNE 40/10 ORAL PELLETS

(Lopinavir 40 mg and Ritonavir 10 mg)

ORAL PELLETS

COMPOSITION:

Each capsule of oral pellets contains lopinavir 40 mg and ritonavir 10 mg as active ingredients.

List of excipients: colloidal silicon dioxide, copovidone, gelatin capsule, hydroxyl propyl methylcellulose, PEG-6000, sodium stearyl fumarate, sorbitan monolaurate and talc.

Capsule ingredients: ammonia solution, black iron oxide, gelatin, iron oxide yellow, potassium hydroxide, propylene glycol, Shellac, sodium dodecyl sulfate and titanium dioxide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Anti-viral agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Lopinavir/ritonavir oral pellets is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. As co-formulated in these oral pellets, ritonavir inhibits the CYP3A4-mediated metabolism of lopinavir, thereby resulting in increased plasma levels of lopinavir.

Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus. HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro.* The presence of ritonavir does not appear to influence the selection of lopinavir resistant viruses *in vitro.* Reduced viral susceptibility to lopinavir has been observed in clinical studies.

Cross-resistance:

Data obtained from four patients previously treated with one or more protease inhibitors who developed increased lopinavir phenotypic resistance during therapy with lopinavir/ritonavir, indicated that patients either remained cross-resistant or developed cross-resistance to ritonavir, indinavir and nelfinavir. All rebound viruses either remained fully sensitive or showed modestly reduced sensitivity to amprenavir (up to 8,5-fold concurrent with 99-fold resistance to lopinavir). Rebound isolates from subjects with no prior exposure to saquinavir remained fully sensitive to saquinavir.

Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a lopinavir-based combination regimen:

Virologic response to lopinavir/ritonavir has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20/M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T and I84V.

Table 1 shows the 48-week virological response (HIV RNA < 400 copies/ ml) according to the number of the above protease inhibitor resistance mutations baseline as observed in clinical studies.

Table 1: Virological response (HIV RNA < 400 copies/ ml) at week 48 by baseline lopinavir/ritonavir susceptibility and number of protease substitutions associated with reduced response to lopinavir/ritonavir[(a)]

Number of protease inhibitor mutations at baseline [(a)]	***Single protease inhibitor-experienced NNRTI-naïve (n= 130) [(b)]***	***Single protease inhibitor-experienced NNRTI-naïve (n= 56) [(c)]***	***Multiple protease inhibitor-experienced NNRTI-niave (n= 50) [(d)]***
0-2	76/103 (74 %)	34/45 (76 %)	19/20 (95 %)
3-5	13/26 (50 %)	8/11 (73 %	18/26 (69 %)
5 or more	0/1 (0 %)	N/A	1/4 (25 %)

a. Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, I54L/T/V, V82A/C/F/S/T and I84V.

b. 43 % indinavir, 42 % nelfinavir, 10 % ritonavir and 15 % saquinavir.

c. 41 % indinavir, 38 % nelfinavir, 4 % ritonavir and 16 % saquinavir.

d. 86 % indinavir, 54 % nelfinavir, 80 % ritonavir and 70 % saquinavir.

Table 2: Virological response (HIV-1 RNA < 50 copies/ ml) at week 48 by baseline number of protease substitutions associated with reduced response to lopinavir/ritonavir.

Number of protease inhibitor mutations at baseline [(a)]	***Treatment-experienced lopinavir/ritonavir once daily + NRTIs (n= 268)*** [(b)]	***Treatment-experienced lopinavir/ritonavir twice daily + NRTIs (n= 264)*** [(c)]
0-2	167/255 (65 %)	154/250 (62 %)
3-5	4/13 (31 %)	8/14 (57 %)
6 or more	N/A	N/A

a. Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, I54L/T/V, V82A/C/F/S/T and I84V.

b. 88 % NNRTI-experienced, 47 % PI-experienced (24 % nelfinavir, 19 % indinavir and 13 % atazanavir).

c. 81 % NNRTI-experienced, 45 % PI-experienced (20 % nelfinavir, 17 % indinavir and 13 % atazanavir).

Pharmacokinetic properties:

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Administration of lopinavir/ritonavir 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15-to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7 % of those obtained after the ritonavir dose of 600 mg twice daily. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of lopinavir/ritonavir is due to lopinavir.

Absorption:

Following multiple dosing with 400/100 mg lopinavir/ritonavir twice daily for three weeks in HIV positive patients with food, mean ± SD lopinavir peak plasma concentration (C_{max}) is 9,8 ± 3,7 microgram/ml, and occurs approximately four hours after administration. The mean steady-state trough concentration prior to the morning dose is 7,1 ± 2,9 mcg/ml. Lopinavir AUC over a 12-hour dosing interval averages 92,6 ± 36,7 mcg/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption

Administration of lopinavir/ritonavir 400/100 mg single dose under fed conditions (high fat meal, 872 kcal, 56 % from fat) compared to the fasted state was associated with no significant changes in C_{max} and AUC_{∞}. Therefore, lopinavir/ritonavir may be taken with or without food. Lopinavir/ritonavir has shown less pharmacokinetic variability under all meal conditions.

Distribution

At steady-state, lopinavir is approximately 98 – 99 % bound to plasma proteins. Lopinavir has a high affinity for alpha-1-acid glycoprotein (AAG), but binds to both AAG and albumin. At steady-state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir/ritonavir twice daily, and is similar between healthy volunteers and HIV-positive patients.

Metabolism:

In vitro studies with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which

inhibits the metabolism of lopinavir, and thereby increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg lopinavir/ ritonavir dose was due to the parent compound. At least 13 lopinavir oxidative metabolites have been identified in man. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but constitute only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 to 14 days.

Elimination

After a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10,4 ± 2,3 % and 82,6 ± 2,5 % of an administered dose of 14C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounts for approximately 2,2 % and 19,8 % of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12-hour dosing interval averages 5 – 6 hours, and the apparent oral clearance of lopinavir is 6 to 7 l/h.

Effects on electrocardiogram

Once daily doses of lopinavir/ritonavir at therapeutic doses may lengthen QTc interval. Modest prolongation of PR interval was observed in patients receiving lopinavir/ritonavir on day 3. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed (see **‘WARNINGS AND SPECIAL PRECAUTIONS’**).

Pharmacokinetics in special populations:

Gender and age

Lopinavir pharmacokinetics have not been studied in the elderly. No age or gender related pharmacokinetic differences were observed in adult patients.

Paediatric patients

The pharmacokinetics of lopinavir/ritonavir 300/75 mg/m^2 twice daily and 230/57,5 mg/m^2 twice daily were studied in paediatric patients, ranging in age from six months to 12 years. The 230/57,5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine showed lopinavir plasma concentrations similar to those obtained in adult patients receiving 400/100 mg twice daily regimen (without nevirapine).

Twice daily doses of lopinavir/ritonavir 230/57,5 mg/m^2 without nevirapine showed lopinavir mean steady-state AUC, C_{max}, and C_{min} of 72,6 ± 31,1 mcg.h/ml, 8,2 ± 2,9 and 3,4 ± 2,1 mcg/ml, respectively, and 85,8 ± 36,9 mcg.h/ml, 10,0 ± 3,3 and 3,6 ± 3,5 mcg/ml, respectively, after 300/75 mg/m^2 twice daily with nevirapine. The nevirapine regimen was 7 mg/kg twice daily (six months to eight years) or 4 mg/kg twice daily (greater than eight years).

Renal insufficiency

Data is not available for patients with renal insufficiency. However, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic insufficiency

Lopinavir is extensively metabolised and eliminated by the liver. Repeated administration of lopinavir/ritonavir 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment increased lopinavir exposure and C_{max} by 30 % and 20 %,

respectively, compared to HIV infected patients with normal liver functioning. Furthermore, lopinavir plasma protein binding was lower in both mild and moderate hepatic impairment than in controls (99,01 vs 99,31 %, respectively). Lopinavir/ritonavir has not been studied in patients with severe hepatic insufficiency (see **'CONTRAINDICATIONS**)**.**

INDICATIONS:

LOPIMUNE 40/10 ORAL PELLETS are indicated in combination with other antiretroviral medicines for the treatment of HIV infection.

CONTRAINDICATIONS:

LOPIMUNE 40/10 ORAL PELLETS are contraindicated in patients with known hypersensitivity to lopinavir, ritonavir or any other ingredients of **LOPIMUNE 40/10 ORAL PELLETS**.
Severe hepatic insufficiency as **LOPIMUNE 40/10 ORAL PELLETS** have not been studied in this condition.

LOPIMUNE 40/10 ORAL PELLETS should not be co-administered with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medicines include medicines listed in Table 3.
LOPIMUNE 40/10 ORAL PELLETS are contraindicated with medicines that are potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance.

Table 3: Medicines which should not be co-administered with LOPIMUNE 40/10 ORAL PELLETS

Class	**Medicine within class not to be co-administered**	**Effect**
Alpha-adrenoreceptor antagonist	Alfuzosin	Potentially increased plasma levels of alfuzosin which can result in hypotension.
Antidysrhythmics	Dronedarone	Potential for cardiac dysrhythmias.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment **(see 'INTERACTIONS').**
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to **LOPIMUNE 40/10 ORAL PELLETS** or to the class of protease inhibitors or other co-administered antiretroviral agents.
Antipsychotics	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Ergot derivatives	Ergotamine, dihydroergotamine, methylergonovine	Potential or to acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.

Class	**Medicine within class not to be co-administered**	**Effect**
Gastrointestinal motility medicines	Cisapride	Potential for cardiac dysrhythmias.
Herbal products	St. John's Wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to **LOPIMUNE 40/10 ORAL PELLETS** or to the class of protease inhibitors.
HMG-CoA reductase inhibitors	Lovastatin Simvastatin	Potential for myopathy including rhabdomyolysis (see **'INTERACTIONS').**
PDE5 enzyme inhibitors	Sildenafil (Contraindicated only when used for the treatment of pulmonary arterial hypertension (PAH))	Potential for sildenafil-associated adverse events including visual abnormalities, hypotension, prolonged erection and syncope.
Sedatives/ hypnotics	Oral midazolam Triazolam	Prolonged or increased sedation and respiratory depression from these sedatives.

WARNINGS AND SPECIAL PRECAUTIONS:

Risk of serious adverse reactions due to interactions with other medicines

Initiation of **LOPIMUNE 40/10 ORAL PELLETS**, a CYP3A inhibitor, in patients receiving medicines metabolised by CYP3A or initiation of medicines metabolised by CYP3A in patients already receiving **LOPIMUNE 40/10 ORAL PELLETS**, may increase plasma concentrations of medicines metabolised by CYP3A. Initiation of medicines that inhibit or induce CYP3A may increase or decrease concentrations of **LOPIMUNE 40/10 ORAL PELLETS**, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicines.
- Clinically significant adverse reactions from greater exposures of **LOPIMUNE 40/10 ORAL PELLETS**.
- Loss of therapeutic effect of **LOPIMUNE 40/10 ORAL PELLETS** and possible development of resistance.

See Table 4 for these possible and known significant medicine interactions (see **'INTERACTIONS'**). Consider the potential for medicine interactions prior to and during **LOPIMUNE 40/10 ORAL PELLETS** therapy; review concomitant medicines during **LOPIMUNE 40/10 ORAL PELLETS** therapy and monitor for the adverse reactions associated with the concomitant medicines (see '**CONTRAINDICATIONS'** and '**INTERACTIONS'**).

Pancreatitis

Pancreatitis has been observed in patients receiving **LOPIMUNE 40/10 ORAL PELLETS** therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to **LOPIMUNE 40/10 ORAL PELLETS** has not been established, marked triglyceride elevations are a risk factor for development of

pancreatitis. Patients with advanced HIV-1 disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during **LOPIMUNE 40/10 ORAL PELLETS** therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and **LOPIMUNE 40/10 ORAL PELLETS** and/or other antiretroviral therapy should be suspended as clinically appropriate.

Hepatotoxicity

Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of **LOPIMUNE 40/10 ORAL PELLETS**.

There have been post-marketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with **LOPIMUNE 40/10 ORAL PELLETS** therapy has not been established.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days after the initiation of **LOPIMUNE 40/10 ORAL PELLETS** in conjunction with other antiretroviral medicines. In some cases, the hepatic dysfunction was serious; however, a definitive causal relationship with **LOPIMUNE 40/10 ORAL PELLETS** therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with **LOPIMUNE 40/10 ORAL PELLETS** and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be considered in the patients with underlying chronic hepatitis or

cirrhosis, especially during the first several months of **LOPIMUNE 40/10 ORAL PELLETS** treatment.

QT interval prolongation

Post-marketing cases of QT interval prolongation and torsade de pointes have been reported although causality of **LOPIMUNE 40/10 ORAL PELLETS** could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalaemia, and with other medicines that prolong the QT interval.

PR interval prolongation

LOPIMUNE 40/10 ORAL PELLETS prolongs the PR interval in some patients. Cases of second- or third-degree atrioventricular block have been reported. **LOPIMUNE 40/10 ORAL PELLETS** should be used with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischaemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. The impact on the PR interval of co-administration of **LOPIMUNE 40/10 ORAL PELLETS** with other medicines that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of **LOPIMUNE 40/10 ORAL PELLETS** with these medicines should be undertaken with caution, particularly with those medicines metabolised by CYP3A. Clinical monitoring is recommended.

Diabetes mellitus/ hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients may require either initiation or dose adjustments of

insulin or oral hypoglycaemic medicines for treatment of these events. Diabetic ketoacidosis may occurr. Hyperglycaemia may persist in those patients who discontinue protease inhibitor therapy. Monitoring of hyperglycaemia, new onset diabetes mellitus or an exacerbation of diabetes mellitus in patients treated with **LOPIMUNE 40/10 ORAL PELLETS** should be considered.

Lipid elevations

Treatment with **LOPIMUNE 40/10 ORAL PELLETS** may result in large increases in the concentration of total cholesterol and triglycerides (see **'SIDE EFFECTS'**). Triglyceride and cholesterol testing should be performed prior to initiating **LOPIMUNE 40/10 ORAL PELLETS** therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential medicine-medicine interactions with **LOPIMUNE 40/10 ORAL PELLETS** and HMG-CoA reductase inhibitors (see **'CONTRAINDICATIONS'** and **'INTERACTIONS'**).

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 and glucose levels in HIV patients. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Haemophilia

Increased bleeding, including spontaneous skin haematomas and haemarthrosis may occur in patients with haemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII may be required. Treatment with protease inhibitors may be continued or reintroduced. Neither a causal relationship nor a mechanism of action between protease inhibitor therapy and these events is known.

Resistance/ cross-resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in **LOPIMUNE 40/10 ORAL PELLETS** -treated patients, it is unknown what effect therapy with **LOPIMUNE 40/10 ORAL PELLETS** will have on the activity of subsequently administered protease inhibitors (see **'PHARMACOLOGICAL ACTION'**).

Immune Reconstitution Inflammatory Syndrome

Immune Reconstitution Inflammatory Syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune response 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 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 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 Grave's 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 **LOPIMUNE 40/10 ORAL PELLETS** 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 **LOPIMUNE 40/10 ORAL PELLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Information for patients

Patients should remain under the care of a doctor while taking **LOPIMUNE 40/10 ORAL PELLETS**. Patients should be advised to take **LOPIMUNE 40/10 ORAL PELLETS** and other concomitant antiretroviral therapy every day as prescribed. **LOPIMUNE 40/10 ORAL PELLETS** must always be used in combination with other antiretroviral medicines. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of **LOPIMUNE 40/10 ORAL PELLETS** is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that **LOPIMUNE 40/10 ORAL PELLETS** are not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of **LOPIMUNE 40/10 ORAL PELLETS** are unknown. Patients should be told that there are currently no data showing that **LOPIMUNE 40/10 ORAL PELLETS** can reduce the risk of transmitting HIV to others through sexual contact. **LOPIMUNE 40/10 ORAL PELLETS** may interact with some medicines; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's Wort (see '**INTERACTIONS'**).

Patients receiving oestrogen-based hormonal contraceptives should be advised to use additional or alternate contraceptive measures during therapy with **LOPIMUNE 40/10 ORAL PELLETS** (see **'INTERACTIONS'**).

Use in the elderly

Caution should be exercised in the administration and monitoring of **LOPIMUNE 40/10 ORAL PELLETS** in elderly patients reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other medicine therapy.

Paediatric use

No safety and pharmacokinetic data are available for **LOPIMUNE 40/10 ORAL PELLETS** in paediatric patients below the age of six months. Studies have demonstrated that the adverse event profile in HIV-infected patients aged 6 months to 12 years is similar to that observed in adult patients.

Effects on ability to drive and use machines

LOPIMUNE 40/10 ORAL PELLETS can cause visual disturbances and drowsiness and can therefore impair the ability to drive or operate machines. Caution is advised.

INTERACTIONS:

LOPIMUNE 40/10 ORAL PELLETS are inhibitors of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of **LOPIMUNE 40/10 ORAL PELLETS** and medicines mainly metabolised by CYP3A (e.g. dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other medicines that could increase or prolong its therapeutic and adverse effects. Medicines that are predominantly metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with **LOPIMUNE 40/10 ORAL PELLETS**. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 3 under **‘CONTRAINDICATIONS’**.

LOPIMUNE 40/10 ORAL PELLETS undergo hepatic metabolism CYP3A. Co-administration of **LOPIMUNE 40/10 ORAL PELLETS** and medicines that induce CYP3A may decrease lopinavir

plasma concentrations and reduce its therapeutic effect. Although not noted with concurrent ketoconazole, co-administration of **LOPIMUNE 40/10 ORAL PELLETS** and other medicines that inhibit CYP3A may increase **LOPIMUNE 40/10 ORAL PELLETS** plasma concentrations.

Based on known metabolic profiles, clinically significant medicine interactions are not expected between **LOPIMUNE 40/10 ORAL PELLETS** and desipramine (CYP2D6 probe), fluvastatin, dapsone, erythromycin or azithromycin and trimethoprim/sulphamethoxazole.

Table 4: Established and other potentially significant medicine interactions

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
HIV-1 antivirals		
HIV-1 protease inhibitor: fosamprenavir/ritonavir	Lowered amprenavir and lopinavir concentrations.	An increased rate of adverse reactions has been observed with co-administration of these medicines.
HIV-1 protease inhibitor: indinavir	Increased indinavir concentration.	Decrease indinavir dose to 600 mg twice daily, when co-administered with lopinavir/ritonavir 400/100 twice daily. Lopinavir/ritonavir once daily has not been studied in combination with indinavir.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
HIV-1 protease inhibitor: nelfinavir	Increased concentrations of nelfinavir and m8 metabolite of nelfinavir. Lowered lopinavir concentration.	Lopinavir/ritonavir once daily in combination with nelfinavir is not recommended.
HIV-1 protease inhibitor: ritonavir	Increased lopinavir concentration.	Appropriate doses of additional ritonavir in combination with **LOPIMUNE 40/10 ORAL PELLETS** have not been established.
HIV-1 protease inhibitor: saquinavir	Increased saquinavir concentration.	The saquinavir dose is 1000 mg twice daily, when co-administered with lopinavir/ritonavir 400/100 mg twice daily. Lopinavir/ritonavir once daily has not been studied in combination with saquinavir.
HIV CCR5 – antagonist: maraviroc	Increased maraviroc concentrations.	When co-administered, patients should receive 150 mg twice daily of maraviroc. For further details see complete prescribing information for maraviroc.
Non-nucleoside reverse	Lowered lopinavir	The dose of lopinavir/ritonavir

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
transcriptase inhibitors: efavirenz and nevirapine	concentrations.	should be increased when co-administered with efavirenz or nevirapine.
Nucleoside reverse transcriptase inhibitor: didanosine	-	It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after **LOPIMUNE 40/10 ORAL PELLETS** (given with food).
Nucleoside reverse transcriptase inhibitor: tenofovir disoproxil fumarate	Increased tenofovir concentrations.	Patients receiving **LOPIMUNE 40/10 ORAL PELLETS** and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside reverse transcriptase inhibitors: abacavir and zidovudine	Lowered concentrations of abacavir and zidovudine.	The clinical significance of this potential interaction is unknown.
Other medicines		
Antidysrhythmics e.g. amiodarone and lidocaine	Increased concentrations of antidysrhythmics.	See '**CONTRAINDICATIONS'** for contraindicated antidysrhythmics.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
(systemic)		Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antidysrhythmics when co-administered with **LOPIMUNE 40/10 ORAL PELLETS**.
Anticancer medicines: vincristine, vinblastine, dasatinib, nilotinib	Increased concentrations of anticancer medicines.	For vincristine and vinblastine, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as **LOPIMUNE 40/10 ORAL PELLETS**. Please refer to the nilotinib and dasatinib prescribing information for dosing

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		instructions.
Anticoagulants: warfarin and rivaroxaban	Increased or decreased warfarin concentrations. Increased rivaroxaban concentrations.	Concentrations of warfarin may be affected. Initial frequent monitoring of the INR (international normalised ratio) during **LOPIMUNE 40/10 ORAL PELLETS** and warfarin co-administration is recommended. Avoid concomitant use of rivaroxaban and **LOPIMUNE 40/10 ORAL PELLETS**. Co-administration of **LOPIMUNE 40/10 ORAL PELLETS** and rivaroxaban may lead to increased risk of bleeding.
Anticonvulsants: carbamazepine, phenobarbitone, phenytoin	Lowered lopinavir and phenytoin concentrations.	**LOPIMUNE 40/10 ORAL PELLETS** may be less effective due to decreased lopinavir concentrations in patients taking these medicines concomitantly and should be used with caution. **LOPIMUNE 40/10 ORAL**

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		PELLETS once daily in combination with carbamazepine, phenobarbitone, or phenytoin is not recommended. In addition, co-administration of phenytoin and **LOPIMUNE 40/10 ORAL PELLETS** may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with **LOPIMUNE 40/10 ORAL PELLETS**.
Anticonvulsants: lamotrigine, valproate	Lowered lamotrigine concentrations. Valproate concentrations may be lowered or remain unchanged.	A dose increase of lamotrigine or valproate may be needed when co-administered with **LOPIMUNE 40/10 ORAL PELLETS** and therapeutic concentration monitoring for lamotrigine may be indicated, particularly during dosage adjustments.
Antidepressant: bupropion	Lowered concentrations of bupropion and its	Patients receiving **LOPIMUNE 40/10 ORAL PELLETS** and

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
	active metabolite, hydroxybupropion.	bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	Increased trazodone concentrations.	Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered.
Anti-infective: clarithromycin	Increased clarithromycin concentrations.	For patients with renal impairment, adjust clarithromycin dose.
Antifungals: ketoconazole, itraconazole and voriconazole	Increased concentrations of ketoconazole and itraconazole. Lowered concentrations of voriconazole.	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. The co-administration of voriconazole and **LOPIMUNE 40/10 ORAL PELLETS** should be avoided.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
		Alternative antifungal therapies should be considered in these patients.
Anti-gout: colchicine	Increased concentrations of colchicine.	Concomitant administration with colchicine is contraindicated in patients with renal and/or hepatic impairment (see '**CONTRAINDICATIONS**').
Antimycobacterial: rifabutin	Increased concentrations of rifabutin and its metabolite.	Dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	Lowered concentrations of atovaquone.	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: quetiapine	Increased concentrations of quetiapine.	*Initiation of* ***LOPIMUNE 40/10 ORAL PELLETS*** *in patients taking quetiapine:* Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures.
Sedative/ hypnotics: parenterally administered	Increased midazolam concentrations.	See '**CONTRAINDICATIONS'** for contraindicated sedatives/

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
midazolam		hypnotics.
Contraceptive: ethinyl estradiol	Lowered concentrations of ethinyl estradiol.	Because contraceptive steroid concentrations may be altered when **LOPIMUNE 40/10 ORAL PELLETS** are co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.
Corticosteroids (systemic): e.g. budesonide, dexamethasone, prednisone	Increased concentrations of glucocorticoids and decreased concentrations of lopinavir.	Use with caution. **LOPIMUNE 40/10 ORAL PELLETS** may be less effective due to decreased lopinavir plasma concentrations in patients taking these medicines concomitantly.
Dihydropyridine calcium channel blockers: e.g. felodipine and nifedipine	Increased concentrations of dihydropyridine calcium channel blockers.	Clinical monitoring of patients is recommended and a dose reduction of the dihydropyridine calcium channel blocker may be considered.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
HMG-CoA reductase inhibitors: atorvastatin and rosuvastatin	Increased concentrations of atorvastatin and rosuvastatin.	See '**CONTRAINDICATIONS'** for contraindicated HMG-CoA reductase inhibitors.
Immunosuppressants: e.g. ciclosporin, tacrolimus and sirolimus	Increased concentrations of immunosuppressants.	Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with **LOPIMUNE 40/10 ORAL PELLETS**.
Inhaled or intranasal steroids e.g.: fluticasone and budesonide	Increased concentrations of glucocorticoids.	Concomitant use of **LOPIMUNE 40/10 ORAL PELLETS** and fluticasone or other glucocorticoids that are metabolised by CYP3A is not recommended.
Long-acting beta-adrenoceptor agonist: salmeterol	Increased concentrations of salmeterol.	Concurrent administration of salmeterol and **LOPIMUNE 40/10 ORAL PELLETS** is not recommended.
Narcotic analgesics: methadone and fentanyl	Decreased concentrations of methadone and increased concentrations	Dosage of methadone may need to be increased when co-administered with **LOPIMUNE**

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
	of fentanyl.	**40/10 ORAL PELLETS**. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with **LOPIMUNE 40/10 ORAL PELLETS**.
PDE5 inhibitors: sildenafil, tadalafil and vardenafil	Increased concentrations of sildenafil, tadalafil and vardenafil.	Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): sildenafil is contraindicated.

PREGNANCY AND LACTATION:

The safety of **LOPIMUNE 40/10 ORAL PELLET**S in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women. The use of **LOPIMUNE 40/10 ORAL PELLETS** during pregnancy is not recommended.

HIV-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving

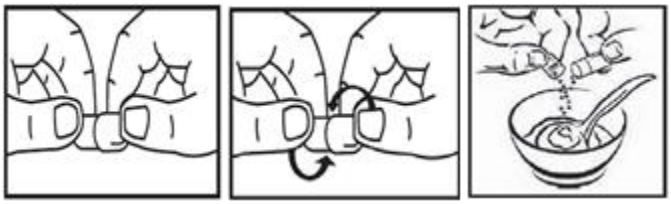
LOPIMUNE 40/10 ORAL PELLETS. It is not known whether lopinavir is secreted in human milk.

DOSAGE AND DIRECTIONS FOR USE:

LOPIMUNE 40/10 ORAL PELLETS should be taken with food.

Method of administration:

Capsules containing the oral pellets should not be swallowed whole but should be administered with food as shown below (capsule contents should be emptied into ready-to-eat-porridge).



- Place sweetened porridge, which is at room temperature, in a small bowl.
- Obtain the prescribed number of capsules needed for a dose.
- Hold both ends of the capsule between your fingertips as depicted above.
- Twist the ends of the capsule in opposite direction and pull apart so that the entire contents of the capsule are sprinkled over the sweetened porridge.
- Repeat this step for the prescribed number of capsules per dose. Ensure that the entire content of each capsule is sprinkled over the porridge.
- This medicine-porridge mixture should be eaten immediately. The oral pellets should not be chewed or crushed. They should not be stored for future use.
- Administration of the required dose should be followed by drinking water, to ensure that no pellets are left behind in the mouth.
- Repeat above steps for next dose.

Adults and children older than 12 years or children less than 12 years who weigh more than 40 kg:

The recommended dose of lopinavir/ritonavir is 400 /100 mg (10 capsules) twice daily with food.

Children: 6 months to 12 years:

The recommended dose of lopinavir/ritonavir in children weighing:

- 7 to 15 kg is 12/3 mg per kg twice daily with food.
- 15 to 40 kg is 10/2,5 mg per kg twice daily with food.

Concomitant therapy with efavirenz, nevirapine, amprenavir and nelfinavir:

A dose increase is required and the recommended dose of lopinavir/ritonavir in children weighing:

- 7 to 15 kg is 13/3,25 mg per kg twice daily with food.
- 15 to 40 kg is 11/2,75 mg per kg twice daily with food.

LOPIMUNE 40/10 ORAL PELLETS should not be administered once daily in patients under 18 years of age.

LOPIMUNE 40/10 ORAL PELLETS should not be administered to neonates before a post-menstrual age (first day of the mother's menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

Table 5: Dosing guideline for LOPIMUNE 40/10 ORAL PELLETS without concomitant efavirenz, nevirapine, amprenavir or nelfinavir. This table lists what is required to be administered twice daily using a simplified weight band approach:

Weight of child	**Recommended dose to be taken twice per day (with food)**
5 kg to less than 6 kg	80/20 mg (2 capsules)
6 kg to less than 10 kg	120/30 mg (3 capsules)
10 kg to less than 14 kg	160/40 mg (4 capsules)
14 kg to less than 20 kg	200/50 mg (5 capsules)
20 kg to less than 25 kg	240/60 mg (6 capsules)
25 kg to less than 30 kg	280/70 mg (7 capsules)
30 kg to less than 35 kg	320/80 mg (8 capsules)
Equal to and greater than 35 kg	Adult dose, 400/100 mg (10 capsules)

Concomitant therapy

Efavirenz, nevirapine, amprenavir and nelfinavir:

The recommended lopinavir/ritonavir dose in patients on concomitant therapy is:

- Patients weighing 7 to 15 kg: 13/3,25 mg/kg twice daily with food.
- Patients weighing 15 to 40 kg: 11/2,75 mg/kg twice daily with food.

Precise dosage titration may not be possible with **LOPIMUNE 40/10 ORAL PELLETS**. An appropriate lopinavir/ritonavir oral solution should be used.

LOPIMUNE 40/10 ORAL PELLETS should not be administered as a once daily regimen in children, whether or not in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

LOPIMUNE 40/10 ORAL PELLETS should not be administered as a once daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir in adults.

Dosing using body surface area (BSA) in m^2

Dosage using BSA is not possible with **LOPIMUNE 40/10 ORAL PELLETS**. Therefore, an appropriate lopinavir/ritonavir oral solution should be used.

Omeprazole and ranitidine:

LOPIMUNE 40/10 ORAL PELLETS may be used in combination with acid reducing medicines, omeprazole and ranitidine. No dose adjustments are required.

SIDE EFFECTS:

Infections and infestation:

Frequent: otitis media, bronchitis, sinusitis, furunculosis, bacterial infections, pharyngitis, flu syndrome, gastroenteritis, sialadenitis, cellulitis, folliculitis, perineal abscess, upper respiratory tract infections.

Neoplasm benign, malignant and unspecified:

Less frequent: benign skin neoplasm, cyst, neoplasm.

Blood and lymphatic system disorders:

Frequent: anaemia, leukopenia, lymphadenopathy, neutropenia.

Less frequent: splenomegaly.

Immune system disorders:

Frequent: hypersensitivity reactions including angioedema and urticaria.

Less frequent: immune reconstitution syndrome.

Endocrine disorders:

Less frequent: male hypogonadism, Cushing's syndrome and hypothyroidism.

Metabolic and nutritional disorders:

Frequent: blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, decreased weight, decreased appetite.
Less frequent: dehydration, oedema, avitaminosis, dehydration, lactic acidosis, obesity, anorexia, weight gain, hyperglycaemia, hyperamylaseaemia, hyperlipasaemia, lipomatosis.

Psychiatric disorders:

Frequent: anxiety.
Less frequent: abnormal dreams, agitation, confusion, depression, emotional lability, libido decreased, nervousness, apathy, mood swings, abnormal thinking.

Nervous system disorders:

Frequent: headache (including migraine), insomnia, neuropathy (including peripheral neuropathy), dizziness.
Less frequent: amnesia, somnolence, dyskinesia, ataxia, encephalopathy, facial paralysis, loss of taste, taste perversion, cerebral infarct, hypertonia, paraesthesia, peripheral neuritis, tremor, convulsions, extrapyramidal syndrome, balance disorder.

Eye disorders:

Less frequent: abnormal vision, eye disorder.

Ear and labyrinth disorders:

Less frequent: vertigo, tinnitus.

Cardiac disorders:

Less frequent: palpitations, pulmonary oedema, angina pectoris, atrioventricular block, arterial fibrillation, myocardial infarction, tricuspid valve incompetence.

Vascular disorders:

Frequent: hypertension.
Less frequent: deep vein thrombosis, thrombophlebitis, varicose vein and vasculitis, vascular disorder, postural hypotension, vasodilation.

Respiratory, thoracic and mediastinal disorders:

Less frequent: bronchitis, otitis media, asthma, dyspnoea, lung oedema, rhinitis, sinusitis, increased cough.

Gastrointestinal disorders:

Frequent: diarrhoea, abdominal pain, abnormal stools, dyspepsia, nausea, vomiting, flatulence, pancreatitis, gastroenteritis, abdominal distension.
Less frequent: enlarged abdomen, taste perversion, cholecystitis, constipation, dry mouth, dysphagia, enterocolitis, enteritis, eructation, oesophagitis, faecal incontinence, flatulence, gastritis, haemorrhagic colitis, duodenitis, gastric ulcer, gastroesophageal reflux disease, increased appetite, mouth ulceration, sialadenitis, stomatitis, ulcerative stomatitis, periodontitis, haemorrhoids, rectal haemorrhage.

Hepato-biliary disorders:

Frequent: hepatitis including AST, ALT and GGT increases.

Less frequent: cholecystitis, cholangitis, jaundice, hepatomegaly, liver fatty deposit, liver tenderness, hyperbilirubinemia.

Skin and subcutaneous tissue disorders:

Frequent: rash (including maculopapular rash), lipodystrophy, acne, rash including eczema and seborrheic dermatitis, pruritus, night sweats.
Less frequent: alopecia, dry skin, eczema, exfoliative dermatitis, face oedema, furunculosis, nail disorder, skin benign neoplasm, skin discolouration, skin ulcer, skin striae, allergic dermatitis, sweating, stretch marks, idiopathic capillaritis, vasculitis, alopecia.
Frequency not known: Steven-Johnson Syndrome, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Frequent: myalgia, back pain, arthralgia, muscle disorders like weakness and spasms.
Less frequent: arthrosis, pain in extremity, bone necrosis, joint disorder, myasthenia, rhabdomyolysis.

Renal and urinary disorders:

Less frequent: kidney calculus, urine abnormality, nephritis, albuminaria, hypercalcinuria, nephritis, hyperuricaemia, haematuria, abnormal urine odour.

Reproductive system and breast disorders:

Frequent: erectile dysfunction, amenorrhoea, menorraghia.

Less frequent: abnormal ejaculation, gynaecomastia, impotence, breast enlargement.

General disorders and administration site conditions:

Frequent: asthenia, pain, fatigue.

Less frequent: chest pain, substernal chest pain, chills, medicine interaction, medicine level increased, oedema, peripheral oedema, fever, malaise.

Investigations:

The following abnormalities have been reported in therapy-naïve adult patients:

Less frequent: increased glucose, uric acid, AST, ALT, GGT, total cholesterol, triglycerides and amylase levels and decreased neutrophils.

The following abnormalities have been reported in therapy-experienced (protease inhibitor) adult patients:

Less frequent: increased glucose, total bilirubin, AST, ALT, GGT, total cholesterol, triglycerides and amylase and decreased inorganic phosphate.

The following abnormalities have been reported in children:

Less frequent: increased total bilirubin, AST, ALT, total cholesterol and amylase levels, and decreased sodium levels, platelet and neutrophil counts.

Post-marketing data:

The following have been reported: hepatitis, toxic epidermal necrolysis, Steven-Johnson syndrome, erythema multiforme, bradydysrhythmia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment of overdose with **LOPIMUNE 40/10 ORAL PELLETS** should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with **LOPIMUNE 40/10 ORAL PELLETS**. If indicated, elimination of unabsorbed medicine should be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since **LOPIMUNE 40/10 ORAL PELLETS** are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

IDENTIFICATION:

White to off-white, circular, biconvex, pellets plain on both sides filled in size “1” hard gelatin capsules that have a clear, transparent body with “414” spin printed in black ink and yellow cap with “CL” spin printed in black ink.

PRESENTATION:

LOPIMUNE 40/10 ORAL PELLETS in capsules are packed in pack sizes of 120’s in white HDPE containers fitted with white HDPE lids, containing two 1 g silica gel dessicants.

STORAGE INSTRUCTIONS:

Store in the original container at or below 30 °C.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

51/20.2.8/0123

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

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

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