PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Lopinavir/Ritonavir 40 mg/ 10 mg granules for oral suspension Mylan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 40 mg lopinavir and 10 mg ritonavir.

Each sachet contains 583 mg of mannitol.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Granules for oral suspension

A white to creamish granular powder filled in a sachet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults and children 6 months and older, weighing over 6 kg.

The choice of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan to treat protease inhibitor-experienced HIV-1 infected patients should be based on individual viral resistance testing and their treatment history (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology:

- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should be initiated by a health care provider experienced in the management of HIV infection.
- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should be given in a twice daily (every 12 hours) dosing regimen. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should not be administered once daily (every 24 hours) to children < 18 years of age.
- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should not be administered to premature neonates (born one month or more before expected date of delivery) until 14 days after their due date.
- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan administered in combination with efavirenz, nevirapine, or nelfinavir in patients younger than 6 months of age is not recommended. Total dose of lopinavir and ritonavir oral granules in paediatric patients should not exceed the recommended adult daily dose of 400/100 mg twice daily.

The recommended dose of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan for children is as follows:

Child's weight	Dose
6 – 9,9 kg	3 sachets twice daily (lopinavir 120 mg/ritonavir 30 mg twice daily)
10 – 13,9 kg	4 sachets twice daily (lopinavir 160 mg/ritonavir 40 mg twice daily)

14 – 19,9 kg	5 sachets twice daily (lopinavir 200 mg/ritonavir 50 mg twice daily)
20 – 24,9 kg	6 sachets twice daily (lopinavir 240 mg/ritonavir 60 mg twice daily)

For patients co-treated with nevirapine or efavirenz, see section 4.5.

Special populations

Hepatic impairment

In HIV-infected patients with mild to moderate hepatic impairment, an approximate 30 % increase in lopinavir exposure has been observed but is not expected to be of clinical relevance (see section 5.2). No data are available in patients with severe hepatic impairment. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan must not be given to these patients (see section 4.3).

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Method of administration

For oral administration.

Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan must be taken with a meal twice daily. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should be sprinkled/mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should not be chewed or crushed.

For infants and young children older than 6 months of age who are able to take soft foods:

1. Determine the number of sachets needed to prepare a dose.

2. Prior to mixing, tap the sachet(s) to move all the granules to the bottom of the sachet(s).

3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.

4. Mixing with soft food such as applesauce or porridge: Using a spoon, mix the entire contents of the Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan sachet(s) with soft food (approximately 1 teaspoon of soft food for 1 sachet; 2 teaspoons for 2 sachets, etc.) in a small cup or bowl. Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the small cup/bowl or spoon, add more soft food to the granules and mix. Then give or take the mixture along with adequate drinking water, to ensure that no granules are left behind in the mouth.

5. Mixing with liquid such as drinking water: Mix the entire contents of the Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan sachet(s) with approximately 5 - 15 ml of drinking water (1 teaspoon of water for 2 sachets; 2 teaspoons of water for 3 to 8 sachets; 3 teaspoons or 1 tablespoon for 10 sachets). Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the spoon, add more liquid (water) and mix. Then give or take the mixture.

6. Administer the medicine/food mixture within 2 hours of preparation. If not administered within 2 hours of preparation, throw away the mixture and prepare a new dose.

7. No mixture of the granules and food is to be stored for later use.

8. Repeat above steps for next dose.

4.3 Contraindications

- Known hypersensitivity to lopinavir, ritonavir or to any of the excipients of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan (see section 6.1).
- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan must not be administered to patients with severe hepatic impairment.
- Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan must not be administered concurrently with medicines with a narrow therapeutic window that are substrates of the isoenzyme CYP3A4, such as alfuzosin, amiodarone, dronedarone, bepridil, quinidine, propafenone, verapamil, lurasidone, pimozide, quetiapine, astemizole, terfenadine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir), oral midazolam, triazolam, clorazepate, diazepam, flurazepam, ergot derivatives, fusidic acid, venetoclax, colchicine, simvastatin and lovastatin, avanafil, sildenafil and vardenafil (non-exhaustive list). Inhibition of CYP3A4 by ritonavir could increase plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see also sections 4.4 and 4.5).
- Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking lopinavir and ritonavir due to the risk of decreased plasma concentrations and reduced clinical effects of lopinavir and ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

Patients with coexisting conditions

Hepatic impairment: Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is contraindicated in patients with severe liver impairment. 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. For concomitant antiviral therapy for hepatitis B or C, refer to the relevant medicine information for these medicines.

Patients with liver dysfunction including chronic hepatitis have 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 should be considered.

Laboratory tests should be conducted before starting treatment with lopinavir and ritonavir and during treatment.

Renal impairment: Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Lopinavir and ritonavir are highly protein bound, therefore it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

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. A causal relationship is likely but a biological explanation has not been elucidated. Patients with haemophilia should therefore be warned of the possibility of increased bleeding.

Specific adverse reactions

Lipid elevations: Treatment with lopinavir and ritonavir has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol should be measured before starting Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and periodically during therapy.

Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders should be managed as clinically appropriate.

Pancreatitis: Cases of pancreatitis have been reported in patients receiving lopinavir and ritonavir. Most of these patients have had a history of pancreatitis or concurrent therapy with other medicines associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormal 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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan therapy should be suspended if pancreatitis is diagnosed (see section 4.8).

Hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these cases hyperglycaemia was severe and also associated with ketoacidosis. Many patients had confounding medical conditions. A causal relation between ritonavir-boosted lopinavir and these events has not been established.

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

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency, typically in the first few weeks or months after initiation of combination antiretroviral treatment, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported in the setting of immune reactivation; however, the reported time to onset is more variable and 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. So far, this disorder has been reported mainly in adults. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

PR interval prolongation: Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Second- or third-degree atrioventricular block has been reported in patients taking lopinavir/ritonavir who have underlying structural heart disease and conduction abnormalities or who are taking medicines that prolong the PR interval (such as verapamil or atazanavir). Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should be used with caution in such patients (see sections 4.8, 5.1 and 5.3).

Warnings on specific interactions with other medicines

Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is likely to increase plasma concentrations of medicines that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicines could increase or prolong their therapeutic effect and adverse events (see sections 4.3 and 4.5).

Bedaquiline and delamanid: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with lopinavir/ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with lopinavir/ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline SmPC). Co-administration of delamanid with a strong inhibitor of CYP3A (as lopinavir/ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.5 and refer to the delamanid professional information).

Rifampicin: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with rifampicin is not recommended. Rifampicin in combination with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan causes large decreases in lopinavir concentrations which may in turn significantly decrease the therapeutic effect of lopinavir. Adequate exposure to lopinavir/ritonavir may be achieved with a higher dose of Lopinavir/Ritonavir 40 mg/10 mg granules for oral

suspension Mylan but this is associated with a higher risk of liver and gastrointestinal toxicity.

HMG-CoA reductase inhibitors: Simvastatin and lovastatin are highly dependent on CYP3A for metabolism; thus concomitant use of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is used concurrently with rosuvastatin or with atorvastatin, which are metabolised to a lesser extent by CYP3A4. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

PDE5 inhibitors: Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with these medicines is expected to substantially increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection (see section 4.5). Concomitant use of avanafil or vardenafil and lopinavir/ritonavir is contraindicated (see section 4.3). Concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is contraindicated (see section 4.3).

QT-interval prolonging medicines: Particular caution must be used when prescribing Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and medicines that prolong QT interval such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan could increase concentrations of the co-administered medicines

and this may increase their associated cardiac adverse events (see also section 4.3 and 4.5). Cardiac events have been reported with lopinavir/ritonavir in preclinical studies: therefore, potential cardiac effects of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan cannot be currently ruled out (see sections 4.8 and 5.3).

Sedative medicines: Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should not be used concomitantly with strongly sedative medicines metabolised by CYP3A, as this may result in excessive effects. Such medicines include fentanyl, meperidine, propoxyphene, diazepam, alprazolam, triazolam and midazolam. Morphine and oxazepam are not metabolised by CYP3A; however, due to induction of glucuronidation, an increased dose of these medicines may be necessary when co-treating with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan.

Hormonal contraceptives: In case of co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with contraceptives containing ethinylestradiol, irrespective of the formulation (e.g. oral or patch), additional barrier or non-hormonal methods of contraception are to be used. The decreased systemic exposure to the oestrogen component may not only reduce contraceptive efficacy but also alter the uterine bleeding profile.

Glucocorticoids: Concomitant use of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and fluticasone or other glucocorticoids that are metabolised by CYP3A4 such as budesonide and fluticasone, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Colchicine: Life-threatening and fatal interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir. Concomitant

administration with colchicine is contraindicated in patients with renal and/or hepatic impairment (see sections 4.3 and 4.5).

Tadalafil: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with tadalafil, indicated for the treatment of pulmonary arterial hypertension, is not recommended. (See section 4.5).

Fusidic acid: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with fusidic acid in osteo-articular infections is not recommended (see section 4.5).

Salmeterol: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with salmeterol is not recommended (see section 4.5).

Rivaroxaban: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with rivaroxaban is not recommended (see section 4.5).

Vorapaxar: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with vorapaxar is not recommended. (See section 4.5).

Riociguat: Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan with riociguat is not recommended. (See section 4.5).

Transmission

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

People taking Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan may still develop infections or other illnesses associated with HIV disease and AIDS.

Excipient warning

Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan contains lopinavir and ritonavir, both of which inhibit the P450 isoform CYP3A *in vitro*. Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and medicines primarily metabolised by CYP3A may increase plasma concentrations of the other medicines, which could increase or prolong its therapeutic and adverse reactions (see section 4.3). Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3).

Lopinavir/ritonavir has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicines metabolised by cytochrome P450 (including CYP2C9 and CYP2C19) enzymes and by glucuronidation. This may lower plasma concentrations and potentially decrease efficacy of co-administered medicines. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in section 4.3.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
HIV-1 antivirals		

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
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.
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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral

Concomitant medicine class: name of medicine	Effect on concentration of lopinavir or concomitant medicine	Clinical comments
		suspension Mylan 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 transcriptase inhibitors: efavirenz and nevirapine	Lowered lopinavir concentrations	The dose of lopinavir/ritonavir should be increased when co-administered with efavirenz or nevirapine.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan (given with food).
Nucleoside reverse transcriptase inhibitor: tenofovir disoproxil fumarate	Increased tenofovir concentrations.	Patients receiving Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan 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		

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Antidysrhythmics e.g. amiodarone and lidocaine (systemic)	Increased concentrations of antidysrhythmics.	See section 4.3 for contraindicated antidysrhythmics. Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antidysrhythmics when co-administered with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and warfarin co- administration is recommended. Avoid concomitant use of rivaroxaban and Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. Co-administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and rivaroxaban may lead to increased risk of bleeding.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Anticonvulsants: carbamazepine, phenobarbitone, phenytoin	Lowered lopinavir and phenytoin concentrations.	Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan may be less effective due to decreased lopinavir concentrations in patients taking these medicines concomitantly and should be used with caution. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan once daily in combination with carbamazepine, phenobarbitone, or phenytoin is not recommended. In addition, co-administration of phenytoin and Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan may cause decreases in steady-state phenytoin

Concomitant medicine class: name of medicine	Effect on concentration of lopinavir or concomitant medicine	Clinical comments
		concentrations. Phenytoin levels should be monitored when co- administering with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan.
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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and therapeutic concentration monitoring for lamotrigine may be indicated, particularly during dosage adjustments.
Antidepressant: bupropion	Lowered concentrations of bupropion and its active metabolite, hydroxybupropion.	Patients receiving Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan and bupropion concurrently should be monitored for an

Concomitant medicine class: name of medicine	Effect on concentration of lopinavir or concomitant medicine	Clinical comments
		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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan 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 section 4.3).
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.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Antipsychotics: quetiapine	Increased concentrations of quetiapine.	*Initiation of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan in patients taking quetiapine:* Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures.
Sedative/ hypnotics: parenterally administered midazolam	Increased midazolam concentrations.	See section 4.3 for contraindicated sedatives/ hypnotics
Contraceptive: ethinyl estradiol	Lowered concentrations of ethinyl estradiol.	Because contraceptive steroid concentrations may be altered when Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan are co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Corticosteroids (systemic): e.g. budesonide, dexamethasone, prednisone	Increased concentrations of glucocorticoids and decreased concentrations of lopinavir.	Use with caution. Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan 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.
HMG-CoA reductase inhibitors: atorvastatin and rosuvastatin	Increased concentrations of atorvastatin and rosuvastatin.	See section 4.3 for contraindicated HMG-CoA reductase inhibitors.

Concomitant medicine class: name of medicine	**Effect on concentration of lopinavir or concomitant medicine**	**Clinical comments**
Immunosuppressants: e.g. ciclosporin, tacrolimus and sirolimus	Increased concentrations of immunosuppressants.	Therapeutic concentration monitoring is recommended for immunosuppressant medicines when co-administered with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan.
Inhaled or intranasal steroids e.g.: fluticasone and budesonide	Increased concentrations of glucocorticoids.	Concomitant use of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan 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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is not recommended.

Concomitant medicine class: name of medicine	Effect on concentration of lopinavir or concomitant medicine	Clinical comments
Narcotic analgesics: methadone and fentanyl	Decreased concentrations of methadone and increased concentrations of fentanyl.	Dosage of methadone may need to be increased when co-administered with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan in pregnant women has not been established, as there are no adequate and well-controlled studies in pregnant women. The use of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan during pregnancy is not recommended.

Breastfeeding

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 Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. It is not known whether lopinavir is secreted in human milk.

Fertility

Animal studies have shown no effects on fertility. No human data on the effect of lopinavir/ritonavir on fertility are available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and adverse reactions of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

a) Summary of adverse effects

The most common adverse reaction associated with lopinavir therapy is diarrhoea, nausea and vomiting, usually at the start of treatment. Also, dyslipidaemia, including

hypertriglyceridaemia and hypercholesterolaemia are common, and may require treatment or discontinuation of the medicine.

Pancreatitis has been reported in patients receiving ritonavir-boosted lopinavir. Furthermore, increases in the PR interval have been reported during therapy with ritonavir-boosted lopinavir (see section 4.4).

b) Tabulated summary of adverse reactions

The following adverse reactions of moderate to severe intensity with possible or probable relationship to lopinavir/ritonavir have been reported. The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (≥ 1/10), common (1/100 to 1/10), uncommon (1/1000 to 1/100) and rare (1/10 000 to 1/1 000). Events shown with a frequency 'Not known' were identified during post-marketing surveillance.

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory-tract infection
	Common	Lower respiratory-tract infection, skin infections including cellulitis, folliculitis and furuncle
Blood and lymphatic system disorders	Common	Anaemia, leucopenia, neutropenia, lymphadenopathy
Immune system disorders	Common	Hypersensitivity including urticaria and angioedema
	Uncommon	Immune reconstitution inflammatory syndrome
Endocrine disorders	Uncommon	Hypogonadism

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
Metabolism and nutrition disorders	Common	Blood glucose disorders including diabetes mellitus, hypertriglyceridaemia, hypercholesterolemia, weight decreased, decreased appetite
	Uncommon	Weight increased, increased appetite
Psychiatric disorders	Common	Anxiety
	Uncommon	Abnormal dreams, libido decreased
Nervous system disorders	Common	Headache (including migraine), neuropathy (including peripheral neuropathy), dizziness, insomnia
	Uncommon	Cerebrovascular accident, convulsion, dysgeusia, ageusia, tremor
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Tinnitus, vertigo
Cardiac disorders	Uncommon	Atherosclerosis such as myocardial infarction, atrioventricular block, tricuspid valve incompetence
Vascular disorders	Common	Hypertension
	Uncommon	Deep-vein thrombosis
Gastrointestinal disorders	Very common	Diarrhoea, nausea
	Common	Pancreatitis (see section 4.4: pancreatitis and lipids), vomiting, gastro-oesophageal reflux disease, gastroenteritis and colitis, abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence
	Uncommon	Gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastritis and rectal haemorrhage, stomatitis and oral ulcers, faecal incontinence, constipation, dry mouth
Hepatobiliary disorders	Common	Hepatitis including AST, ALT and GGT increases

Undesirable effects in clinical and post-marketing studies in adults and paediatric patients		
System organ class	**Frequency**	**Adverse reaction**
	Uncommon	Hepatic steatosis, hepatomegaly, cholangitis, hyperbilirubinemia
	Not known	Jaundice
Skin and subcutaneous tissue disorders	Common	Rash including maculopapular rash, dermatitis/rash including eczema and seborrheic dermatitis, night sweats, pruritus
	Uncommon	Alopecia, capillaritis, vasculitis
	Not known	Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Common	Myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms
	Uncommon	Rhabdomyolysis, osteonecrosis
Renal and urinary disorders	Uncommon	Creatinine clearance decreased, nephritis, haematuria
Reproductive system and breast disorders	Common	Erectile dysfunction, menstrual disorders - amenorrhoea, menorrhagia
General disorders and administration site conditions	Common	Fatigue including asthenia

c) Description of selected adverse reactions

Cushing's syndrome has been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide (see section 4.4 and 4.5).

Increased creatine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (see section 4.4).

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

d) Paediatric populations

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-ontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Therapy

There is no specific antidote for overdose with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan. Treatment of overdose with Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan is general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, unabsorbed active substance may be eliminated by emesis. Activated charcoal may also be used to aid removal of unabsorbed active substance. Since lopinavir and ritonavir are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antivirals for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR10

Mechanism of action: Lopinavir provides the antiviral activity of Lopinavir/Ritonavir Granules for Oral suspension 40 mg/10 mg. Lopinavir inhibits the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes. In the absence of human serum, the mean IC_{50} of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50 % human serum, the mean IC_{50} of lopinavir against HIV-1_{IIIB} in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean IC_{50} of lopinavir was 6,5 nM against several HIV-1 clinical isolates. Lopinavir also has *in vitro* activity against HIV-2, with median IC_{50} values similar to those for HIV-1.

Antiviral activity according to genotypic/phenotypic resistance: De novo resistance in treatment-naïve patients with prior wild-type virus failing therapy with ritonavir-boosted lopinavir in combination with NRTI is rare, provided that the patient is regularly monitored for viral load (e.g. 2–4 times annually after attaining undetectable HIV-RNA). For instance, in the pivotal phase 3 trial of ritonavir-boosted lopinavir, 0/51 patients failing therapy had emergent protease inhibitor resistance mutations. Lack of resistance to lopinavir was confirmed by phenotypic analysis. Also, the level of resistance to the backbone therapy has been lower in previously treatment-naïve patients failing on ritonavir-boosted lopinavir therapy, compared with regimens not including a ritonavir-boosted PI.

In patients who have previously failed protease inhibitor therapy, incremental resistance may occur upon virological failure. Mutations V82A, I54V and M46I have emerged most frequently. Mutations L33F, I50V, V32I and I47V/A have also occurred.

The *in vitro* antiviral activity of lopinavir against 112 clinical isolates taken from patients failing therapy with one or more protease inhibitors was assessed. Within this panel, the following mutations in the HIV protease were associated with reduced

in vitro susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC_{50} of lopinavir against isolates with 0–3, 4–5, 6–7 and 8–10 mutations at the above amino acids was 0,8; 2,7; 13,5 and 44-fold higher than the EC_{50} against wild-type HIV, respectively. In addition to the mutations described above, mutations V32I and I47A have been observed in rebound isolates with reduced lopinavir susceptibility form protease inhibitor-experienced patients receiving ritonavir-boosted lopinavir therapy.

In studies of PI-experienced, NNRTI-naïve patients receiving therapy including ritonavir-boosted lopinavir, efavirenz and NRTIs, plasma HIV-RNA < 400 copies was observed at 48 weeks in 93 % (25/27), 73 % (11/15) and 25 % (2/8) of patients with < 10-fold, 10 to 40-fold and > 40-fold reduced susceptibility to lopinavir at baseline. In another study with a dataset from several clinical trials and cohorts, the changes in medicine susceptibility associated with a 20 % and 80 % loss of predicted wild-type medicine effect for lopinavir were 9,7- and 56-fold, respectively.

Clinically relevant resistance to lopinavir requires accumulation of resistance mutations in the HIV-protease. Several genotypic resistance algorithms have been proposed for the quantification of the degree of phenotypic resistance to lopinavir, and for predicting the clinical response to lopinavir in protease inhibitor pre-treated patients. One of these, the lopinavir-ATU score, includes mutations at the following codons of the protease: 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84.

With increasing resistance to lopinavir, resistance to other protease inhibitors will also increase to a varying degree, depending on the pattern of resistance mutations. Viruses with clinically relevant resistance to lopinavir are often susceptible to darunavir or tipranavir (refer to the professional information of these darunavir or tipranavir-containing medicines for information on genotypic predictors of response).

Table 1 Clinical cut-off values for reduced activity of ritonavir-boosted lopinavir by baseline genotype/phenotype

	Activity not affected	Decreased activity	Resistance
LPV-ATU score[1] (no of mutations)	0 – 2	3 – 5	≥ 6
Clinical cut off Phenotype (fold change)[2]	< 10	10 – 60	> 60

1: Codons 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84

2: These are approximate values; see text above. Assay: Antivirogram; Virco.

Clinical efficacy: Ritonavir-boosted lopinavir has been extensively studied in treatment-naïve and treatment-experienced adults and children**.** In various studies in treatment-naïve adults, the combination of ritonavir-boosted lopinavir and 2 NRTIs have yielded response rates (i.e. plasma viral load > 400 or > 50 copies/ml) in the ITT population in the range of 70–80 % at 48 weeks. In treatment-experienced patients the response rate varies depending on the activity of the background regimen and the sensitivity of the virus to lopinavir (see above).

Effects on the electrocardiogram: QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95 % upper confidence bound) differences in QTcF from placebo were 3,6 (6,3) and 13,1 (15,8) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily ritonavir-boosted lopinavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1,5- and 3-fold higher than those with recommended once daily or twice daily lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving

lopinavir/ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11,6 ms to 24,4 ms in the 12-hour interval after dosing. Maximum PR interval was 286 msec and no second- or third-degree heart block was observed (see section 4.4).

5.2 Pharmacokinetic properties

The absorption characteristics of Lopinavir/Ritonavir Granules for Oral suspension 40 mg/10 mg have been determined after administration of single dose granules in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**	
	Lopinavir	**Ritonavir**
Maximum concentration (C_{max})	482 (± 328) ng/mL	31 (± 16) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	4,490 (± 3,584) ng·h/mL	0,275 (± 0,160) ng·h/mL
Time to attain maximum concentration (Tmax)	5,46 (± 1,53) hours	4,89 (± 0,54) hours

Lopinavir is almost completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of ritonavir-boosted lopinavir 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 Granules for Oral suspension 40 mg/10 mg is due to lopinavir.

Absorption

Multiple dosing with 400/100 mg lopinavir/ritonavir twice daily for 2 weeks and without meal restriction produced a mean (SD) lopinavir peak plasma concentration (C_{max}) of 12,3 (5,4) µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8,1 (5,7) µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 113,2 (60,5) µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Distribution

At steady state, lopinavir is approximately 98−99 % bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. Lopinavir has been detected in cerebrospinal fluid at concentrations exceeding the IC_{50} of wild-type virus and has been shown to reduce HIV-RNA in cerebrospinal fluid.

Biotransformation

In vitro experiments indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir and therefore increases plasma levels of lopinavir. At least 13 metabolites of lopinavir have been identified, two of which are active; however, these are present at very low levels. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline during multiple dosing, stabilising after 10 days to 2 weeks.

Elimination

After administering radio-labelled lopinavir with ritonavir, approximately 10 % and 83 % of an administered dose was accounted for 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 averaged 5–6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6–7 litre/hour.

Special populations

Paediatrics: There are limited pharmacokinetic data in children below 2 years of age.

Gender, race and age: Lopinavir/ritonavir pharmacokinetics have not been studied in the elderly. No age-, gender- or race-related effect has been observed in adult patients.

Renal insufficiency: Ritonavir-boosted lopinavir pharmacokinetics has not been studied in 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: The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple-dose study with lopinavir/ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30 % has been observed, and is not expected to be of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acesulfame potassium

Copovidone

Colloidal silicon dioxide

Ethyl cellulose

Mannitol

Sodium stearyl fumarate

Sorbitan monolaurate

Vanilla flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Sachets, comprises of printed triple laminated roll with aluminium foil, soft, dull side PET and bright side laminated to PE film. 1 000 mg granules per sachet.

Pack size: 120 sachets per carton.

6.6 Special precautions for disposal and other handling

No special precautions are required.

For detail instructions on administration of Lopinavir/Ritonavir 40 mg/10 mg granules for oral suspension Mylan, see section 4.2.

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBER

56/20.2.8/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 September 2023

10 DATE OF REVISION OF THE TEXT

TBA