SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lopinavir + Ritonavir Tablets 100 + 25mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Lopinavir……..100mg
Ritonavir……...25mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Pale yellow colored, capsule shaped, biconvex, film-coated tablets debossed with "M31" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Lopinavir + Ritonavir Tablet is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected children.

The choice of Lopinavir + Ritonavir Tablets to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients.

4.2 Posology and method of administration

Lopinavir/Ritonavir tablets 100 mg/25 mg should be prescribed by physicians who are experienced in the treatment of HIV infection.

In patients weighing <15 kg, the recommended dose is 12 mg lopinavir/3 mg ritonavir/kg BW given twice daily
In patients weighing 15-35 kg, the recommended dose is 10 mg lopinavir /2.5 mg ritonavir /kg BW given twice daily
In patients weighing > 35 kg, the adult dose of 400 mg lopinavir/100 mg ritonavir given twice daily should be used.

The following table contains dosing guidelines for Lopinavir/Ritonavir tablets 100 mg/25 mg, in accordance with WHO guidelines.

Body weight	Recommended number of 100/25 mg tablets	
	morning	evening
10-13.9 kg	2	1
14-19.9 kg	2	2
20-24.9 kg	3	2
25-35 kg	3	3
> 35 kg	Use adult formulation (lopinavir/ritonavir 200/50 mg)	

In children co treated with nevirapine or efavirenz the following doses should be used

For patients weighing <15 kg, 13/3.25 mg/kg should be given twice daily
For patients weighing >15 kg, 11/2.75 mg/kg should be given twice daily

The doses should be taken approximately 12 hours apart.
Lopinavir/Ritonavir tablets 100 mg/25 mg tablets may be taken with or without food
Lopinavir/Ritonavir tablets 100 mg/25 mg tablets should be swallowed whole and not chewed, broken or crushed.

Children weighing less than 10 kg:
Lopinavir/ritonavir is not recommended for use in children weighing less than 10 kg due to insufficient data on safety and efficacy.

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. No data are available in patients with severe hepatic impairment. Lopinavir/Ritonavir tablets 100 mg/25 mg must not be given to these patients.

Renal impairment: No dose adjustment is necessary in patients with renal impairment. Caution is warranted when Lopinavir/Ritonavir tablets 100 mg/25 mg is used in patients with severe renal impairment.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Patients with severe hepatic insufficiency.

Lopinavir and Ritonavir both are inhibitors of the P450 isoform CYP3A. They should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include:

Medicinal product class	Medicinal products within class	Rationale
Concomitant medicinal product levels increased		
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension. The concomitant administration with alfuzosin is contraindicated.
Antiarrthymics	Amiodarone	Increased plasma concentrations of amiodarone. Thereby, increasing the risk of arrhythmias or other serious adverse reactions.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid. The concomitant administration with fusidic acid is contraindicated in dermatological infections.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/ Neuroleptics	Pimozide	Increased plasma concentrations of pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from this agent.
Ergot alkaloids	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.
HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis.
Phosphodiesterase (PDE5) inhibitors	Sildenafil,	Contraindicated when used for the treatment of pulmonary arterial

		hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope).
	Vardenafil	Increased plasma concentrations of vardenafil
Sedatives/hypnotics	Oral midazolam, triazolam	Increased plasma concentrations of oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents.
Lopinavir/ritonavir medicinal product level decreased		
Herbal products	St. John's wort	Herbal preparations containing St John's wort (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of lopinavir and ritonavir.

Other agents:
Lopinavir/Ritonavir tablets 100 mg/25 mg tablets must not be administered concurrently with agents with a narrow therapeutic window that are substrates of CYP3A4, such as bepedril, quinidine, propafenone and verapamil.

4.4 Special warnings and precautions for use

Patients with coexisting conditions:
Hepatic impairment: Lopinavir/Ritonavir tablets 100 mg/25 mg 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. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

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 had been evoked, although the mechanism of action had not been elucidated. Haemophiliac patients should therefore be made aware 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 testing is to be performed prior to initiating Lopinavir/Ritonavir tablets 100mg /25mg therapy and at periodic intervals during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate.

Pancreatitis: Cases of pancreatitis have been reported in patients receiving lopinavir and ritonavir. Most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products 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 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 Lopinavir/Ritonavir tablets 100mg /25mg therapy should be suspended if a diagnosis of pancreatitis is made.

Hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing 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.

Fat redistribution and metabolic disorders: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between protease inhibitors (PIs) and visceral lipomatosis, and between certain nucleoside reverse transcriptase inhibitors (NRTIs), mainly stavudine and zidovudine, and lipoatrophy, seems likely given available evidence. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome: In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, 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.

Osteonecrosis: Although the etiology 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 disease 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. Rarely, 2nd or 3rd degree atroventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir.
Lopinavir/Ritonavir tablets 100mg /25mg should be used with caution in such patients.

Warnings on specific interactions with other medicinal products
Lopinavir/Ritonavir tablets 100mg /25mg contains ritonavir, which is a very potent inhibitor of the P450 isoform CYP3A. Lopinavir/Ritonavir tablets 100mg /25mg is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events.

Rifampicin: Co-administration of Lopinavir/Ritonavir tablets 100mg /25mg with rifampicin is not recommended.
Rifampicin in combination with Lopinavir/Ritonavir tablets 100mg /25mg 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 when a higher dose of Lopinavir/Ritonavir tablets 100mg /25mg is used 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 tablets 100mg /25mg 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 tablets 100mg /25mg 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.

QT-interval prolonging agents: Particular caution must be used when prescribing Lopinavir/Ritonavir tablets 100mg /25mg and medicinal products known to induce QT interval prolongation. Lopinavir/Ritonavir tablets 100mg /25mg could increase concentrations of the coadministered medicinal products and this may result in an increase of their associated cardiac adverse events.

Sedative agents: Lopinavir/Ritonavir tablets 100mg /25mg should not be used concomitantly with strongly sedative drugs metabolized by CYP3A, as this may result in excessive effects. Such drugs include, among others, fentanyl, meperidine, propoxiphene, diazepam, alprazolam, triazolam and midazolam. Morphine and oxazepam are not metabolized by CYP3A; however, due to induction of glucuronidation, an increased dose of these drugs may be necessary when co-treating with Lopinavir/Ritonavir tablets 100mg /25mg.

Hormonal contraceptives: In case of co-administration of Lopinavir/Ritonavir tablets 100mg /25mg with contraceptives containing ethinyl oestradiol, 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 estrogen component may not only impact the contraceptive efficacy but also lead to alterations in the uterine bleeding profile.

Glucocorticoids: Concomitant use of Lopinavir/Ritonavir tablets 100mg /25mg and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Other
Treatment with Lopinavir/Ritonavir tablets 100mg /25mg mg has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer. Patients should continue to use appropriate precautions to prevent transmission of HIV.
People taking Lopinavir/Ritonavir tablets 100mg /25mg may still develop infections or other illnesses associated with HIV disease and AIDS.

4.5 Interaction with other medicinal products and other forms of interaction

Lopinavir/Ritonavir tablets 100mg /25mg contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A *in vitro*. Co-administration of Lopinavir/Ritonavir tablets 100mg /25mg and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions. Lopinavir/Ritonavir tablets 100mg /25mg does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Lopinavir/ritonavir has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450

enzymes and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products.

The following list of drug interactions with Lopinavir/Ritonavir tablets 100mg /25mg is not exhaustive, but is a selection of interactions of putative importance.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Stavudine	Not studied, but no interaction expected	No dose adjustment necessary.
Lamivudine	Not studied, but no interaction expected	No dose adjustment necessary.
Emtricitabine	Not studied, but no interaction expected	No dose adjustment necessary.
Zidovudine	No clinically relevant interaction expected	No dose adjustment necessary.
Abacavir (600 mg q.d.)	Abacavir AUC ↓ 30%	No dose adjustment recommended.
Tenofovir (300 mg q.d.)	Tenofovir AUC ↑ 30%	No dose adjustment recommended. Renal function should be monitored.
Efavirenz (600 mg q.d./ lopinavir/ritonavir tablets 400/100 b.i.d)	Lopinavir AUC ↓ 30-40%	In adults, a 25% dose increase of lopinavir/ritonavir is recommended.
Nevirapine (200 mg b.i.d)	Lopinavir AUC ↓ 27%, Cmin ↓ 51% compared to historical data	In adults, a 25% dose increase of lopinavir/ritonavir is recommended.
Etravirine (1600 mg b.i.d.)	Lopinavir AUC ↓ 20% Etravirine AUC ↑ 17%	No dose adjustment necessary.
Raltegravir (400 mg b.i.d)	Lopinavir AUC ↔ Raltegravir AUC ↓ 30%	No dose adjustment necessary.
Maraviroc (300 mg b.i.d)	Maraviroc AUC ↑ 3.95-fold	In adults, it is recommended that the maraviroc dose be reduced by 50% when co-treating with lopinavir/ ritonavir.
Enfuvirtide	Not studied, but no interaction expected.	No dose adjustment necessary.
Atazanavir (300mg q.d.)	Atazanavir	The benefit of co-administering

	AUC unchanged, Cmin ↑ 45% (compared to atazanavir/ ritonavir 300/100 mg q.d.) Lopinavir AUC unaltered	two protease inhibitors (excepting ritonavir as a pharmacokinetic boosting agent) has not been demonstrated. Furthermore, appropriate doses of HIV protease inhibitors in combination with lopinavir/ritonavir with respect to safety and efficacy have not been established. Therefore, generally coadministration of lopinavir/ritonavir with other PIs is not recommended. If concomitant administration of Lopinavir/Ritonavir tablets 100mg /25mg with PIs is considered necessary, this requires close monitoring.
Darunavir/ritonavir (1200/100 mg q.d.)	Darunavir AUC ↓ 41%, Cmin ↓ 45% compared to darunavir/ ritonavir 600/100 mg b.i.d.) Lopinavir AUC unaltered.	
Fosamprenavir/ritonavir (700/100 b.i.d.)	Amprenavir AUC ↓ 63%, Cmin ↓ 65% Lopinavir AUC ↑ 37%, Cmin ↑ 52%	
Indinavir (600mg q.d.)	Indinavir AUC unaltered, Cmin ↑ 3.5-fold (compared to indinavir 800 mg t.i.d.). Lopinavir AUC unaltered.	
Nelfinavir (1000 mg b.i.d.)	Lopinavir AUC ↓ 27%, Cmin ↓ 38% Nelfinavir AUC ↑ 7%, Cmin ↑ 86% (compared to nelfinavir 1250 mg b.i.d.)	
Saquinavir (800 mg b.i.d.)	Saquinavir AUC ↑ 30% (compared to saquinavir/ ritonavir 1000/100 mg b.i.d.)	
Tipranavir/ritonavir (500/200 mg b.i.d)	Lopinavir AUC ↓ 47%, Cmin ↓ 70%	
Anti-Mycobacterial		
Rifampicin (600 mg q.d.; lopinavir/ritonavir SGC 400/100 mg b.i.d.) Rifampicin (600 mg; lopinavir/ritonavir SGC 800/200 b.i.d.)	Lopinavir AUC ↓ 75%, Cmin ↓ 99% Lopinavir AUC unchanged, Cmin ↓ 54% compared to lopinavir/ ritonavir 400/100 mg without rifampicin.	The co-administration of Lopinavir/Ritonavir tablets 100mg /25mg and rifampicin is not recommended. Rifabutin is the preferable rifamycin in this situation. In adults, if co-administration is judged unavoidable, a dose adjustment of lopinavir/ritonavir to 400/400 mg twice daily has

Rifampicin (600 mg q.d.; lopinavir/ritonavir SGC 400/400 mg b.i.d.)	Lopinavir AUC unchanged, Cmin ↓ 10%, compared to lopinavir/ ritonavir 400/100 mg without rifampicin	allowed compensating for the CYP3A4- inducing effect of rifampicin. Also in children, dosing lopinavir and ritonavir at a 1:1 dose ratio has been evaluated. The ritonavir dose should be titrated upward only after rifampicin has been initiated. Patients should be carefully monitored for side effects and therapeutic efficacy
Rifabutin (150 mg q.d.)	Rifabutin AUC ↑ 3-fold; 25-O-deacetylrifabutin (active metabolite) AUC ↑ 47.5-fold, compared with rifabutin 300 mg q.d.	In adults rifabutin dose should be reduced by 75%; i.e. to 150 mg every other day, or 150 mg thrice weekly, and safety should be closely monitored. No studies on rifabutin dosing when co-treating with lopinavir/ritonavir in children are available.
Other anti-infectives		
Clarithromycin (500 mg b.i.d., together with ritonavir 200 mg t.i.d.)	Chlarithromycin AUC ↑ 77%; 14-OH-clarithromycin (active metabolite) AUC ↓ 100%	Clarithromycin doses greater than 1g/day should not be coadministered with Lopinavir/Ritonavir tablets 100mg /25mg. For patients with renal impairment, a clarithromycin dose reduction should be considered.
Erythromycin	No interaction data available. Erythromycin levels may increase	Co-administer with caution and monitor for adverse effects.
Fusidic acid	No interaction data available. Exposure to fusidic acid is expected to increase.	Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and systemically administered fusidic acid should be avoided as this may result in hepatotoxicity.
Vorizonazole (200 mg b.i.d., together with ritonavir 100 mg b.i.d)	Voriconazole AUC ↓ 39%	Coadministration of Lopinavir/ Ritonavir tablets 100mg /25mg and voriconazole should be avoided due to the risk of therapeutic failure secondary to low voriconazole exposure. If

		deemed necessary, the therapeutic effect of voriconazole should be carefully monitored, and plasma concentration measured, if feasible
Itraconazole		Itraconazole exposure may increase. Doses > 200 mg/d are not recommended.
Ketoconazole		Itraconazole exposure may increase. Doses > 200 mg/d are not recommended.
Fluconazole		No interaction expected.
Sulfamethoxazole/trimethoprim		No interaction expected.
Atovaquone		Atovaquone exposure may decrease. The therapeutic effect should be carefully monitored.
Artemisinin derivatives		No data are available. However artemisinin derivatives are metabolized into active metabolites by CYP3A. The putative interaction effects are unclear. If co-administered, monitor efficacy and safety of artemisinins
Halofantrine		Halofantrine prolongs the QT interval and is metabolized by CYP3A. Coadministration with Lopinavir/Ritonavir tablets 100mg /25mg is contraindicated.
Lumefantrine (480 mg b.i.d.)	Lumefantrine AUC ↑ 193%	Lumefantrine and Lopinavir/ Ritonavir tablets 100mg /25mg should be co-administered with caution.
Quinine (600 mg single dose, ritonavir 200 mg b.i.d)	Quinine AUC and Cmax ↑ 4-fold (Pharmacokinetic interaction between ritonavir and quinine.	Since quinine may prolong the QT-interval, co-administration should be avoided unless the benefit is considered to outweigh the risk.
Sulfadoxine/pyrimethamine	Not studied, but no interaction expected.	No dose adjustment necessary.
Doxycycline	Not studied, but no	No dose adjustment necessary.

	interaction expected.	
Chloroquine	Chloroquine levels may increase due to CYP3A inhibition.	Co-administer with caution and monitor for chloroquine toxicity.
Mefloquine	Not studied, but no interaction expected.	No dose adjustment necessary.
Analgesics		
Buprenorphine (16 mg q.d.)	Buprenorphine and norbuprenorphine AUC ↔	No dose adjustment necessary.
Methadone (5 mg single dose)	Methadone AUC ↓ 53%	Monitor for methadone withdrawal symptoms, and increase methadone dose if necessary.
Morphine	Morphine levels may be decreased due to induction of glucuronidation.	Dose increase may be necessary to maintain therapeutic effect.
Fentanyl, Propoxiphene		Lopinavir/Ritonavir tablets 100mg /25mg co-administration is likely to result in increased plasma concentrations of fentanyl and propoxiphene, and is therefore contraindicated
Meperidine		The concomitant use of Lopinavir/ Ritonavir tablets 100mg /25mg and meperidine is contraindicated due to increases in concentrations of the metabolite normeperidine which may increase the risk of CNS side effects (e.g. seizures).
Antiarrhythmics		
Amiodarone Bepridil Quinidine Propafenone		Co-administration with Lopinavir/ Ritonavir tablets 100mg /25mg is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone and quinidine, and is therefore contraindicated.
Digoxin (0.4 mg SD + ritonavir 200 mg b.i.d.)	Digoxin AUC: ↑ 22%. Ritonavir may increase digoxin levels due to modification of P-	Careful monitoring of digoxin levels is recommended when digoxin is

	glycoprotein mediated digoxin efflux.	administered concomitantly with Lopinavir/Ritonavir tablets 100mg /25mg.
Antiasthmatic		
Theophylline		An increased dose of theophylline may be required due to induction of CYP1A2. Monitor clinical efficacy and theophylline plasma concentration if possible.
Anticancer Agents		
Ifosfamide Vincristine Vinblastine Etoposide	Serum concentrations of ifosfamide, vincristine, vinblastine and etoposide may be increased due to CYP3A inhibition.	This may results in an increase in the incidence and severity of adverse events. These agents and Lopinavir/ Ritonavir tablets 100mg /25mg should be co-administered with caution.
Anticoagulant		
Warfarin		S-warfarin levels may be decreased leading to reduced anticoagulation due to induction of CYP1A2 and CYP2C9 by ritonavir. However, in some patients with aberrant metabolism, warfarin effect may increase Dose alterations of warfarin may be necessary, and INR should be monitored closely.
Anticonvulsants		
Carbamazepine	Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and carbamazepine could lead to a two-way interaction, with increased plasma levels of carbamazepine (due to CYP3A inhibition) and decreased levels of lopinavir (due to hepatic enzyme induction).	Coadministration should be avoided. If deemed necessary, monitor clinical efficacy and safety, and plasma concentrations of carbamazepine and lopinavir if possible.
Phenytoin	Co-administration of	Co-administration should be

	Lopinavir/ Ritonavir tablets 100mg /25mg and phenytoin may lead to a two way interaction, with decreased levels of both phenytoin and lopinavir.	avoided. If deemed necessary, monitor clinical efficacy, and plasma concentrations of phenytoin and lopinavir if possible.
Lamotrigine (100 mg b.i.d)	Lamotrigine AUC ↓ 50%	Monitor efficacy and, if possible, lamotrigine plasma concentration. A dose increase of lamotrigine may be necessary.
Phenobarbital		Coadministration should be avoided, as decreased levels of lopinavir may result due to hepatic enzyme induction by phenobarbital. If coadministration is deemed necessary, monitor efficacy and, if possible, plasma levels of lopinavir.
Valproic acid	Probably no clinically relevant interaction.	Monitor efficacy and safety. Probably no dose adjustment will be necessary
Antidepressants		
Trazodone (50 mg single dose; ritonavir 200 mg b.i.d.)	Trazodone AUC ↑ 2.4-fold	If trazodone is co-administered with Lopinavir/Ritonavir tablets 100mg /25mg, the combination should be used with caution, intiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.
Antipsychotics		
Pimozide		Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and pimozide is contraindicated, as inhibition of CYP3A may increase the plasma concentration of pimozide.
Clozapine		Co-administer with caution, as Lopinavir/ Ritonavir tablets 100mg /25mg may increase plasma levels of clozapine.
Antihistamines		

Astemizole Terfenadine		Co-administration with Lopinavir/ Ritonavir tablets 100mg /25mg is likely to result in increased plasma concentrations of astemizole and terfenadine, and is therefore contraindicated.
Calcium channel blockers		
Verapamil		Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and verapamil is contraindicated, as increased verapamil plasma levels could cause AV-block
Diltiazem		Lopinavir/Ritonavir tablets 100mg /25mg and diltiazem should not be coadministered, as increased diltiazem plasma levels could cause AV-block.
Amlodipine Felodipine Nifedipine		Coadminister with caution. Careful monitoring of adverse effects is recommended when co-administering Lopinavir /Ritonavir tablets 100mg /25mg and amlodipine, felodipine, nifedipine or other dihydropyridine calcium channel blockers, since CYP3A blockade by Lopinavir/ Ritonavir tablets 100mg /25mg may cause higher plasma levels of these drugs.
Hmg-COA reductase inhibitors		
Simvastatin Lovastatin		Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg is contraindicated, as this is likely to lead to increased plasma levels of simvastatin or lovastatin and, thus, to a greater risk of rhabdomyolysis.
Atorvastatin (20 mg q.d.)	Atorvastatin AUC ↑ 5.9-fold	If co-administered, the lowest possible initial dose of atorvastatin should be used, and

		the patient should be closely monitored for efficacy and safety.
Rosuvastatin (20 mg q.d.)	Rosuvastatin AUC ↑ 2.1-fold	If co-administered, the lowest possible initial dose of rosuvastatin should be used, and the patient should be closely monitored for efficacy and safety.
Pravastatin (20 mg q.d.)	Pravastatin AUC ↑ 33%	No dose adjustment necessary.
Fluvastatin	No clinically relevant interaction expected	No dose adjustment necessary.
Immunosuppressants		
Cyclosporine A	Following initiation of ritonavir-boosted PI treatment, a dose reduction of cyclosporine A to 5-20% of prior dose was needed to maintain cyclosporine A levels within therapeutic range.	Co-administer only, if therapeutic drug monitoring of cyclosporine is available. Reduce cyclosporine dose and monitor plasma concentrations closely.
Tacrolimus	The tacrolimus dose, needed to maintain therapeutic concentrations, have often been < 2% when co-administered with a boosted PI, compared to when tacrolimus was given without a PI.	Co-administer only if therapeutic drug monitoring of tacrolimus is available. Reduce tacrolimus dose and monitor plasma concentrations closely.
Hormonal Contraceptives		
Ethinylestradiol 0.035 mg Norethindrone 1 mg	Ethinylestradiol AUC ↓ 42% Norethindrone AUC ↓ 17%	Due to reductions in ethinyl oestradiol concentrations, contraceptive efficacy may be impaired. (Additional) barrier or other non-hormonal methods of contraception should be used.
PDE5 Inhibitors		
Sildenafil (100 mg SD, ritonavir 500 mg b.i.d.)	Sildenafil AUC ↑ 11-fold	Coadminister with caution. Sildenafil doses should not exceed 25 mg in 48 hours.
Tadalafil (20 mg SD; ritonavir	Tadalafil	Coadminister with caution.

200 mg b.i.d.)	AUC ↑ 124%	Tadalafil doses should not exceed 10 mg every 72 hours.
Vardenafil (5 mg single dose; ritonavir 600 mg b.i.d)	Vardenafil AUC ↑ 49-fold	Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and vardenafil is contraindicated.
Sedatives/Hypnotics		
Triazolam (0.125 mg SD; ritonavir 200 mg, 4 doses)	Triazolam AUC ↑ > 20-fold (no steady state)	Lopinavir/Ritonavir tablets 100mg /25mg co-administration is likely to result in increased plasma concentrations of triazolam, and is therefore contraindicated.
Clorazepate Diazepam Estazolam Flurazepam		Lopinavir/Ritonavir tablets 100mg /25mg co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam, through inhibition of CYP3A, and is therefore contraindicated.
Midazolam	Midazolam AUC(oral) ↑ 13-fold AUC (parenteral) ↑ 4-fold	Co-administration of Lopinavir/ Ritonavir tablets 100mg /25mg and oral midazolam is contraindicated. If Lopinavir/Ritonavir tablets 100mg /25mg is coadministered with parenteral midazolam, it should be done in an intensive care unit or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. A reduced dose should be considered, especially if more than a single dose of midazolam is administered.
Alprazolam	Alprazolam metabolism was inhibited following the introduction of	Caution is warranted during the first several days when alprazolam is

	ritonavir. After ritonavir use for 10 days, no inhibitory effect was observed.	coadministered with Lopinavir/ Ritonavir tablets 100mg /25mg, before induction of alprazolam metabolism develops.
Oxazepam	Due to induction of glucuronidation, oxazepam clearance may be increased	Monitor oxazepam efficacy and increase dose if necessary.
Steroids		
Fluticasone propionate aqueous nasal spray (0.2 mg q.d; ritonavir 100 mg b.i.d.)	Fluticasone AUC ↑ 350-fold	Concomitant administration of Lopinavir/Ritonavir tablets 100mg /25mg and fluticasone or other inhaled corticosteroids (e.g. budesonide, mometasone) that are substrates of CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. The use of a corticosteroid which is not a substrate of CYP3A (e.g. beclomethasone) should be preferred.
Prednisolone (20 mg SD; ritonavir 200 mg b.i.d.)	Prednisolone AUC ↑ 30%	Monitor for corticosteroid efficacy and side effects and dose adjust if necessary.
Miscellaneous		
Alfuzosin	Lopinavir/Ritonavir tablets 100mg /25mg is likely to increase plasma concentrations of alfuzosin.	The combination should be avoided.
Dihydroergotamine Ergonovine Ergotamine Methylergovine		Co-administration of ergot derivatives and Lopinavir/Ritonavir tablets 100mg /25mg is contraindicated, as this is likely to lead to increased plasma levels of the ergot derivatives.
Cisapride		Co-administration of cisapride and Lopinavir/Ritonavir tablets 100mg /25mg is contraindicated, as this is likely to lead to increased plasma

		levels of cisapride.
St John's Wort		Serum levels of lopinavir may decrease due to concomitant use of the herbal preparation St John's Wort. Co-administration is contraindicated.

4.6 Pregnancy and lactation

Pregnancy: Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown, but available data do not support a teratogenic potential in humans. Lopinavir/Ritonavir tablets 100mg /25mg should only be used in pregnancy if the benefit clearly outweights the risk.

Lactation: Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. It is recommended that HIV-infected mothers should not breast-feed in order to avoid the transmission of HIV. Only under specific circumstances the benefits of breast-feeding might be considered to outweigh the risks. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter.

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. Patients should be informed that nausea has been reported during treatment with Lopinavir plus Ritonavir Tablet.

4.8 Undesirable effects

The most common adverse reaction associated with lopinavir therapy is diarrhoea and was generally of mild to moderate severity. Also, dyslipidaemia, including hypertriglyceridaemia and hypercholesterolaemia are common, and may require drug treatment or discontinuation of Lopinavir/Ritonavir tablets 100mg /25mg.

It is important to note that cases of pancreatitis have been reported in patients receiving ritonavir boosted lopinavir. Furthermore, rare increases in the PR interval have been reported during therapy with ritonavir-boosted lopinavir.

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).

Undesirable effects in clinical studies in adult patients

Investigations:
Very common (Grade 3 or 4): Blood triglycerides increased, blood cholesterol increased, glutamyltransferase increased
Common (Grade 3 or 4): Blood glucose increased, blood amylase increased, aspartate aminotransferase increased, alanine aminotransferase increased, liver function tests abnormal
Uncommon: Glucose tolerance decreased, blood bilirubin increased, creatinine renal clearance decreased, lipase increased, weight increased, weight decreased, hormone level abnormal, laboratory test abnormal
Rare: Blood alkaline phosphatase increased

Cardiac disorders:
Uncommon: Myocardial infarction1, palpitations
Rare: Atrioventricular block

Blood and lymphatic system disorders:
Uncommon: Anaemia, leucopenia, lymphadenopathy
Rare: Splenomegaly

Nervous system disorders:
Common: Headache, paraesthesia
Uncommon: Extrapyramidal disorder, migraine, facial palsy, encephalopathy, dizziness, amnesia, coordination abnormal, hypertonia, neuropathy, neuropathy peripheral, somnolence, tremor, ageusia, dysgeusia, dyskinesia

Eye disorders:
Uncommon: Visual disturbance
Ear and labyrinth disorders:
Uncommon: Tinnitus
Rare: Vertigo, hyperacusis

Respiratory, thoracic and mediastinal disorders:
Uncommon: Pulmonary oedema, dyspnoea, cough

Gastrointestinal disorders:
Very common: Diarrhoea
Common: Nausea, vomiting, abdominal pain, abnormal faeces, dyspepsia, flatulence, gastrointestinal disorder
Uncommon: Haemorrhagic colitis, pancreatitis, enterocolitis, oesophagitis, constipation, faecal incontinence, abdominal distension, gastrooesophageal reflux disease, dry mouth, dysphagia, eructation, gastritis, mouth ulcerations, stomatitis, periodontitis
Rare: Haemorrhoids

Renal and urinary disorders:
Uncommon: Nephrolithiasis, nephritis, albuminuria, hypercalcinuria, urine abnormality

Skin and subcutaneous tissue disorders:
Common: Rash, lipodystrophy acquired, acne
Uncommon: Alopecia, eczema, dermatitis exfoliative, rash maculopapular, dermatitis allergic, dry skin, nail disorder, pruritis, seborrhoea, skin discoloration, skin ulcer, hyperhidrosis, skin striae
Rare: Idiopathic capillaritis

Musculoskeletal and connective tissue disorders:
Uncommon: Arthralgia, osteoarthritis, myalgia, back pain, arthropathy

Endocrine disorders:
Uncommon: Cushing syndrome, hypothyroidism, hypogonadism male,

Metabolism and nutrition disorders:
Uncommon: Diabetes mellitus, dehydration, lactic acidosis, oedema, increased appetite, obesity, anorexia, hyperglycaemia, hypocholesteraemia, lipomatosis, hyperuricaemia, hypovitaminosis
Rare: Hypophosphataemia, decreased appetite

Infections and infestations:
Uncommon: Gastroenteritis, otitis media, bronchitis, sinusitis, sialadenitis, furunculosis, bacterial infection, viral infection, pharyngitis, influenza, rhinitis
Rare: Cellulitis, folliculitis, perineal abscess

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Uncommon: Benign neoplasm of skin

Vascular disorders:
Uncommon: Hypertension, thrombophlebitis, deep vein thrombosis, vasculitis, varicose vein, angiopathy

General disorders and administration site conditions:
Common: Asthenia, pain
Uncommon: Chest pain, chest pain substernal, chills, pyrexia, malaise, oedema peripheral, face oedema, drug interaction, cyst

Immune system disorders:
Uncommon: Drug hypersensitivity
Rare: Immune reconstitution syndrome

Hepatobiliary disorders:
Uncommon: Hepatitis, cholecystitis, hepatic steatosis, hepatomegaly, liver tenderness

Reproductive system and breast disorders:
Uncommon: Amenorrhoea, menorrhagia, ejaculation disorder, erectile dysfunction, breast enlargement, gynaecomastia

Psychiatric disorders:
Common: Insomnia
Uncommon: Agitation, anxiety, confusional state, depression, affect lability, abnormal dreams, decreased libido, nervousness, abnormal thinking

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

Undesirable effects in clinical studies in paediatric patients

Infections and infestations:
Common: Viral infection

Nervous system disorders:
Common: Taste perversion

Gastrointestinal disorders:
Common: Constipation, vomiting, pancreatitis

Hepatobiliary disorders:
Common: Hepatomegaly

Skin and subcutaneous tissue disorders:
Common: Rash, dry skin

General disorders and administration site conditions:
Common: Fever

Investigations:
Common (Grade 3 or 4): Increased activated partial thromboplastin time, decreased haemoglobin, decreased platelets, increased sodium, increased potassium, increased calcium, increased bilirubin, increased ALT, increased AST, increased total cholesterol, increased amylase, increased uric acid, decreased sodium, decreased potassium, decreased calcium, decreased neutrophils.

4.9 Overdose

To date, there is limited human experience of acute overdose with lopinavir/ritonavir.

There is no specific antidote for overdose with Lopinavir/Ritonavir tablets 100mg /25mg. Treatment of overdose with Lopinavir/Ritonavir tablets 100mg /25mg is to consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in 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: protease inhibitor, ATC code: J05AE06

Mechanism of action:
Lopinavir provides the antiviral activity of Lopinavir/Ritonavir tablets 100mg /25mg. Lopinavir is an inhibitor of 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, respectively. In the absence of human serum, the mean IC50 of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50% human serum, the mean IC50 of lopinavir agaist HIV-1_{IIIB} in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean IC50 of lopinavir was 6.5 nM against several HIV-1 clinical isolates. Lopinavir also has in vitro activity against HIV-2, with median IC50 values similar to those seen 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 three 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, when 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.

Clinically relevant resistance to lopinavir requires the 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 pretreated 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.

5.2 Pharmacokinetic properties

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 EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Lopinavir/Ritonavir tablets 200 mg/50 mg is due to lopinavir.

Absorption

Following single dose Lopinavir/Ritonavir tablets 200 mg/50 mg administration in healthy volunteers under fasting conditions, the mean lopinavir C_{max} value was 7669.136 ng/ml, the corresponding value for AUC_{0-t} was 102339.059 ng*h/ml, $AUC_{0-\infty}$ was 110836.596 ng*h/ml and for t_{max} it was 3.698 hours.

The mean ritonavir C_{max} value was 632.535 ng/ml, the corresponding value for AUC_{0-t} was 5197.070 ng*h/ml, $AUC_{0-\infty}$ was 5473.539 ng*h/ml and for t_{max} it was 3.754 hours.

Following single dose Lopinavir/Ritonavir tablets 200 mg/50 mg administration in healthy volunteers under fed conditions, the mean lopinavir C_{max} value was 7775.383 ng/ml, the corresponding value for AUC_{0-t} was 122403.353 ng*h/ml, $AUC_{0-\infty}$ was 128760.832 ng*h/ml and for t_{max} it was 6.317 hours.

The mean ritonavir C_{max} value was 746.301 ng/ml, the corresponding value for AUC_{0-t} was 6451.417 ng*h/ml, $AUC_{0-\infty}$ was 6646.931 ng*h/ml and for t_{max} it was 5.90 hours.

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 IC50 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 with time 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.

Following single dose Lopinavir/Ritonavir tablets 200 mg/50 mg administration in healthy volunteers under fasting conditions, the $t_{1/2}$ of Lopinavir is 6.02671 hrs and of Ritonavir is 5.55938 hrs.

Following single dose Lopinavir/Ritonavir tablets 200 mg/50 mg administration in healthy volunteers under fed conditions, the $t_{1/2}$ of Lopinavir is 5.24537 hrs and of Ritonavir is 4.86013 hrs.

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 have 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.

5.3 Preclinical safety data

Repeat-dose toxicity studies in rodent and dogs identified major target organs including the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. The exposures eliciting these changes were comparable to or below human clinical exposure. Mild renal tubular degeneration was confined to mice exposed to at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyorxine levels led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but

not other species. Serum Cholesterol was elevated in rodents but not dogs, while triglyceriges were elevated only in mice.

During *in vitro* studies, cloned human cardiac potassium channels (hERG) were inhibited by 30% at the highest concentrations of lopinavir/ritonavir tested, corresponding to a lopinavir exposure 15-fold the free peak plasma levels achieved in humans at the maximum recommended therapeutic dose. In contrast, similar concentrations of lopinavir/ritonavir demonstrated no repolarisation delay in the canine cardiac Purkinje fibres. Lower concentrations of lopinavir/ritonavir did not produce significant potassium (hERG) current blockade. Tissue distribution studies conducted in the rat did not suggest significant cardiac retention of the active substance; 72-hour AUC in heart was approximately 50% of measured plasma AUC. Therefore, it is reasonable to expect that cardiac lopinavir levels would not be significantly higher than plasma levels. In dogs, prominent U waves on the electrocardiogram have been observed associated with prolonged PR interval and bradycardia. These effects have been assumed to be caused by electrolyte disturbance. The clinical relevance of these preclinical data is unknown, however, the potential cardiac effects of this product in humans cannot be ruled out.

In rats, embryofoetotoxicity (pregnancy loss, decreased foetal viability, decreased foetal body weights, increased frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans.

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumours, generally considered to have little relevance to human risk.
Carcinogenicity studies in rats revealed no tumourigenic findings. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The active ingredient is Lopinavir and Ritonavir

The other ingredients are:
Copovidone, Sorbitan Monolaurate, Colloidal Silicon Dioxide, Anhydrous Dibasic Calcium Phosphate, Colloidal Silicon Dioxide, Sodium Stearyl Fumarate, coloring agency contains, polyvinyl alcohol-part hydrolyzed, Titanium dioxide, Polyethylene Glycol, Talc, Iron oxide Yellow.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage
Keep out of the reach and sight of children.

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container
60s Container Pack : 60 tablets packed in 75cc heavy weight HDPE container, 38 mm Child –resistant closure along with the pack insert.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Supplier

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8. WHO Reference Number (Prequalification Programme)
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9. Date of First Prequalification
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10. Date of Revision of the Text:

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2. http://www.medicines.org.uk/EMC/medicine/18442/SPC/Kaletra+200+mg+50+mg+film-coated+tablets/
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