PROPOSED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES (AND DOSAGE FORM):

RILOVIA 100/25 (film-coated tablets)

RILOVIA 200/50 (film-coated tablets)

COMPOSITION:

RILOVIA 100/25:

Each film-coated tablet contains 100 mg lopinavir and 25 mg ritonavir.

Sugar free

RILOVIA 200/50:

Each film-coated tablet contains 200 mg lopinavir and 50 mg ritonavir.

Sugar free

List of Excipients:

Sodium stearyl fumarate, colloidal silicon dioxide, copovidone, sorbitan monolaurate, film-coat {hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, iron oxide yellow, talc, polyethylene glycol 3350, polysorbate 80, colloidal anhydrous silica}

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Mechanism of action:

Lopinavir provides the antiviral activity of **RILOVIA 100/25 and RILOVIA 200/50** tablets. 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 IC_{50} of lopinavir against five different HIV-1 laboratory strains ranged from 10 – 27 nM. In the presence of 50 % human serum, the mean IC_{50} of lopinavir against these live laboratory strains ranged from 68 – 289 nM.

Resistance:

In vitro selection of resistance:

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. HIV-1 has been passaged *in vitro* with lopinavir alone and with lopinavir plus ritonavir at concentration ratios representing the range of plasma concentration ratios observed during lopinavir and ritonavir therapy. Genotypic and phenotypic analysis of viruses selected in these passages suggests that the presence of ritonavir, at these concentration ratios, does not measurably influence the selection of lopinavir-resistant viruses.

Cross-resistance:

Activity of other protease inhibitors against isolates that developed incremental resistance to lopinavir after lopinavir/ritonavir tablets therapy in protease inhibitor experienced patients: The presence of cross-resistance to other protease inhibitors was analysed in 18 rebound isolates that had demonstrated evolution of resistance to lopinavir during 3 Phase II and one Phase III studies of lopinavir/ritonavir tablets in protease inhibitor-experienced patients. The median fold IC_{50} of lopinavir for these 18 isolates at baseline and rebound was 6,9- and 63-fold, respectively, compared to wild type virus. In general, rebound isolates either retained (if cross-resistant at baseline) or developed significant cross-resistance to indinavir, saquinavir and atazanavir. Modest decreases in amprenavir activity were noted with a median increase of IC_{50} from 3,7- to 8-fold in the baseline and rebound isolates, respectively. Isolates retained susceptibility to tipranavir with a median increase of IC_{50} in baseline and rebound isolates of 1,9- and 1,8–fold, respectively, compared to wild type virus.

Pharmacokinetic properties:

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of lopinavir/ritonavir tablets 400/100 mg twice daily yielded 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 tablets is due to lopinavir.

Absorption:

Multiple dosing with 400/100 mg lopinavir/ritonavir tablets twice daily for 3 to 4 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9,6 ± 4,4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5,5 ± 4,0 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 82,8 ± 44,5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption*:*

Administration of a single 400/100 mg dose of lopinavir/ritonavir tablets under fed conditions (high fat, 872 kcal, 56 % from fat) compared to fasted state was associated with no significant changes in C_{max} and AUC_{inf}. Therefore, lopinavir/ritonavir tablets may be taken with or without food.

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. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg lopinavir/ritonavir tablets twice daily, and is similar between healthy volunteers and HIV-positive patients.

Metabolism:

In vitro experiments with human hepatic microsomes 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. A ^{14}C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir tablets dose was due to parent substance. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 to 16 days.

Elimination:

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

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 limit) 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 LPV/r, respectively. The induced QRS interval prolongation from 6 ms to 9,5 ms with high dose lopinavir/ritonavir (800/200 mg twice daily) contributes to QT prolongation. The two regimens resulted in exposures on Day 3 which were approximately 1,5 and 3-fold higher than those observed with recommended once daily or twice daily LPV/r 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 post dose. Maximum PR interval was 286 msec and no second or third degree heart block was observed.

Special Populations

Paediatrics:

There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of lopinavir/ritonavir oral solution 300/75 mg/m^2 twice daily and 230/57,5 mg/m^2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady state AUC, C_{max}, and C_{min} were 72,6 ± 31,1 µg•h/ml, 8,2 ± 2,9 µg/ml and 3,4 ± 2,1 µg/ml, respectively after lopinavir/ritonavir oral solution 230/57,5 mg/m^2 twice daily without nevirapine (n=12), and were 85,8 ± 36,9 µg•h/ml, 10,0 ± 3,3 µg/ml and 3,6 ± 3,5 µg/ml, respectively after 300/75 mg/m^2 twice daily with nevirapine (n=12). The 230/57,5 mg/m^2 twice daily regimen without nevirapine and the 300/75 mg/m^2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine.

Gender, Race and Age:

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

Renal Insufficiency:

Lopinavir/ritonavir tablets 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 % and 20 % in Cmax has been observed.

INDICATIONS:

RILOVIA 100/25 and RILOVIA 200/50 are indicated for the treatment of HIV-1 infected adults, in combination with other antiretroviral agents.

Most experience with lopinavir/ritonavir tablets is derived from the use of the product in antiretroviral therapy naïve patients. Data in heavily pretreated protease inhibitor experienced patients are limited. There are limited data on salvage therapy on patients who have failed therapy with **RILOVIA 100/25 and RILOVIA 200/50**.

CONTRA-INDICATIONS:

Hypersensitivity to the active substances or to any of the excipients in **RILOVIA 100/25 and RILOVIA 200/50** tablets.

Patients with severe hepatic insufficiency.

RILOVIA 100/25 and RILOVIA 200/50 contain lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. **RILOVIA 100/25 and RILOVIA 200/50** 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 astemizole, midazolam, triazolam, cisapride, pimozide, amiodarone, ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine), vardenafil, sildenafil, salmeterol, lovastatin, simvastatin.

Sildenafil only when used for the treatment of pulmonary arterial hypertension (PAH).

Herbal preparations containing St. John's Wort (*Hypericum perforatum)* must not be used while taking **RILOVIA 100/25 and RILOVIA 200/50** due to the risk of decreased plasma concentrations and

reduced clinical effects of **RILOVIA 100/25 and RILOVIA 200/50**.

WARNINGS:

Patients with co-existing conditions:

Liver disease:

The safety and efficacy of **RILOVIA 100/25 and RILOVIA 200/50** have not been established in patients with significant underlying liver disorders. **RILOVIA 100/25 and RILOVIA 200/50** are contra-indicated 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 events. 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. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship 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.

Lipid elevations:

Treatment with **RILOVIA 100/25 and RILOVIA 200/50** may result in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating **RILOVIA 100/25 and RILOVIA 200/50** 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/ritonavir such as contained in **RILOVIA 100/25 and RILOVIA 200/50** tablets, including those who developed hypertriglyceridaemia. In some cases fatalities have been observed. 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 should occur. Patients who exhibit these signs or symptoms should be evaluated and **RILOVIA 100/25 and RILOVIA 200/50** 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 the hyperglycaemia was severe and in some cases also associated with ketoacidosis. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases.

Fat redistribution and metabolic disorders:

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients. These may manifest as redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (‘buffalo hump’), peripheral wasting, facial wasting, breast enlargement and ‘Cushingoid’ appearance. The long-term consequences of these events are unknown. Knowledge about the mechanism is incomplete.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine 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 severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymtomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal
mycobacterial infections and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment 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 in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

PR interval prolongation:

Lopinavir and ritonavir such as in **RILOVIA 100/25 and RILOVIA 200/50** have been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atroventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. **RILOVIA 100/25 and RILOVIA 200/50** should be used with caution in such patients.

RILOVIA 100/25 and RILOVIA 200/50 are not a cure for HIV infection or AIDS. It does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Appropriate precautions

should be taken. Patients taking **RILOVIA 100/25 and RILOVIA 200/50** may still develop infections or other illnesses associated with HIV disease and AIDS.

INTERACTIONS:

RILOVIA 100/25 and **RILOVIA 200/50** contain lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. **RILOVIA 100/25** and **RILOVIA 200/50** are likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases o plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events.

RILOVIA 100/25 and **RILOVIA 200/50** have 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 o efficacy of co-administered medicinal products.

Medicinal products that are contra-indicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in the **CONTRA-INDICATIONS** section**.**

Antiretroviral agents:

Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs):

Stavudine and lamivudine:

No change in the pharmacokinetics of lopinavir was observed when **RILOVIA 100/25 and RILOVIA 200/50** tablets were given alone or in combination with stavudine and lamivudine in clinical studies.

Didanosine:

It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be co-administered with **RILOVIA 100/25 and RILOVIA 200/50** without food.

Zidovudine and abacavir:

RILOVIA 100/25 and RILOVIA 200/50 induce glucuronidation, therefore **RILOVIA 100/25 and**

RILOVIA 200/50 have the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir:

When tenofovir disoproxil fumarate was co-administered with **RILOVIA 100/25 and RILOVIA 200/50** tablets, tenofovir concentrations were increased by approximately 30 % with no changes noted in lopinavir or ritonavir concentrations. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz:

In a study performed in healthy volunteers to explore the interaction between **RILOVIA 100/25 and RILOVIA 200/50** tablets (400/100 mg twice daily) and efavirenz (600 mg once daily), efavirenz has been shown to decrease the lopinavir concentrations by 30 – 40 %. When **RILOVIA 100/25 and RILOVIA 200/50** dosages were increased to 500/125 mg twice daily during co-administration of efavirenz 600 mg once daily in healthy volunteers, lopinavir pharmacokinetic parameters were similar to those obtained with **RILOVIA 100/25 and RILOVIA 200/50** tablets 400/100 mg twice daily administered alone. Therefore, the **RILOVIA 100/25 and RILOVIA 200/50** dosage should be increased to 500/125 mg twice daily when co-administered with efavirenz 600 mg once daily.

Increasing the dose of **RILOVIA 100/25 and RILOVIA 200/50** to 600/150 mg twice daily co-administered with efavirenz significantly increased lopinavir plasma concentrations by approximately 36 % and_ritonavir concentrations by approximately 56 % to 92 % compared to **RILOVIA 100/25 and RILOVIA 200/50** 400/100 mg twice daily without efavirenz.

Nevirapine:

Similar pharmacokinetic interactions are expected for the co-administration of **RILOVIA 100/25 and RILOVIA 200/50** with the NNRTI nevirapine and with the protease inhibitors nelfinavir and amprenavir. That is decreases in the concentration of lopinavir and increases in the concentrations of nevirapine, nelfinavir and amprenavir. The same recommendations for monitoring apply in these cases of co-administration.

Co-administration with other HIV protease inhibitors (PIs):

Amprenavir:

See recommendations described for **RILOVIA 100/25 and RILOVIA 200/50** co-administration with amprenavir.

Fosamprenavir:

Co-administration of standard doses of **RILOVIA 100/25 and RILOVIA 200/50** with fosamprenavir results in a significant reduction in amprenavir concentrations. Co-administration of increased doses of fosamprenavir (1400 mg twice daily) with lopinavir/ritonavir 533/133 mg twice daily to protease inhibitor-experienced patients resulted in a higher incidence of gastrointestinal adverse events and elevations in triglycerides with the combination regimen without increases in virological efficacy, when compared with standard doses of fosamprenavir/ritonavir. Therefore, concomitant administration of these medicinal products is not recommended.

Indinavir:

Indinavir 600 mg twice daily in combination with **RILOVIA 100/25 and RILOVIA 200/50** tablets produced similar indinavir AUC, higher C_{min} (by 3,5-fold) and lower C_{max} relative to indinavir 800 mg three times daily alone.

Nelfinavir:

RILOVIA 100/25 and RILOVIA 200/50 are expected to increase concentrations of nelfinavir and increase the M8 metabolite of nelfinavir (nelfinavir 1000 mg twice daily plus **RILOVIA 100/25 and RILOVIA 200/50** produced similar AUC, similar Cmax, increased Cmin relative to nelfinavir 1250 mg twice daily). Co-administration of **RILOVIA 100/25 and RILOVIA 200/50** and nelfinavir resulted in decreased concentrations of lopinavir. **RILOVIA 100/25 and RILOVIA 200/50** should not be administered once daily in combination with nelfinavir.

Saquinavir:

Saquinavir 800 mg twice daily co-administered with **RILOVIA 100/25 and RILOVIA 200/50** produced

an increase of saquinavir AUC by 9,6-fold relative to saquinavir 1200 mg three times daily given alone.

Ritonavir:

RILOVIA 100/25 and RILOVIA 200/50 tablets co-administered with an additional 100 mg ritonavir twice daily resulted in an increase of lopinavir AUC and C_{min} of 33 % and 64 %, respectively, as compared to **RILOVIA 100/25 and RILOVIA 200/50** tablets alone.

Other medicinal products:

Antidysrhythmics (amiodarone, bepridil, systemic lidocaine and quinidine):

Concentrations may be increased when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. Caution is warranted and therapeutic concentration monitoring is recommended when available (see **CONTRA-INDICATIONS**).

Digoxin:

Plasma concentrations of digoxin may be increased when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. Caution is warranted and therapeutic monitoring of digoxin concentrations, if available, is recommended in case of co-administration of **RILOVIA 100/25 and RILOVIA 200/50** and digoxin. Particular caution should be used when prescribing **RILOVIA 100/25 and RILOVIA 200/50** in patients taking digoxin as the acute inhibitory effect of ritonavir on Pgp is expected to significantly increase digoxin levels.

Dihydropyridine calcium channel blockers: (e.g. felodipine, nifedipine, nicardipine):

May have their serum concentrations increased by **RILOVIA 100/25 and RILOVIA 200/50**.

Anticoagulants:

Warfarin concentrations may be affected when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. It is recommended that INR (international normalised ratio) be monitored.

Medicines that prolong QT interval:

Particular caution must be used when prescribing **RILOVIA 100/25 and RILOVIA 200/50** and medicinal

products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. **RILOVIA 100/25 and RILOVIA 200/50** tablets could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse events. Cardiac events have been reported with **RILOVIA 100/25 and RILOVIA 200/50** tablets in preclinical studies; therefore, the potential cardiac effects of **RILOVIA 100/25 and RILOVIA 200/50** cannot be currently ruled out.

Anticancer agents (e.g. vincristine, vinblastine):

These agents may have their serum concentrations increased when co-administered with **RILOVIA 100/25 and RILOVIA 200/50,** resulting in the potential for increased adverse events usually associated with these anticancer agents.

Anticonvulsants (phenobarbital, phenytoin, carbamazepine):

Will induce CYP3A4 and may decrease lopinavir concentrations.

In addition, co-administration of phenytoin and **RILOVIA 100/25 and RILOVIA 200/50** resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with **RILOVIA 100/25 and RILOVIA 200/50**.

Antidepressants:

Bupropion:

In healthy volunteers, the AUC and C_{max} of bupropion and of its active metabolite, hydroxybupropion, were decreased by about 50 % when co-administered with **RILOVIA 100/25 and RILOVIA 200/50** 400/100 mg twice daily at steady-state. Therefore, if the co-administration of **RILOVIA 100/25 and RILOVIA 200/50** with bupropion is judged unavoidable, this should be done under close clinical monitoring for bupropion efficacy, without exceeding the recommended dosage, despite the observed induction.

Trazodone:

In a pharmacokinetic study performed in healthy volunteers, concomitant use of low dose ritonavir (200

mg twice daily) with a single dose of trazodone led to an increase in plasma concentrations of trazodone (AUC increased by 2,4-fold). Adverse events of nausea, dizziness, hypotension and syncope were observed following co-administration of trazodone and ritonavir in a clinical study. **RILOVIA 100/25 and RILOVIA 200/50** should be used with caution and a lower dose of trazodone should be considered.

Midazolam:

Midazolam is extensively metabolised by CYP3A4. Co-administration with **RILOVIA 100/25 and RILOVIA 200/50** may cause a large increase in the concentration of midazolam. A phenotyping cocktail study in 14 healthy volunteers showed an increase of AUC by about 13-fold with oral midazolam and an increase by about 4-fold with parenteral midazolam. Therefore, **RILOVIA 100/25 and RILOVIA 200/50** tablets co-administered with orally administered midazolam are contra-indicated and caution should be exercised with co-administration of **RILOVIA 100/25 and RILOVIA 200/50** and parenteral midazolam. If **RILOVIA 100/25 and RILOVIA 200/50** tablets are co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered especially if more than a single dose of midazolam is administered (see **CONTRA-INDICATIONS**).

HMG-CoA reductase inhibitors:

HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with **RILOVIA 100/25 and RILOVIA 200/50** are contra-indicated (see **CONTRA-INDICATIONS)**. Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with **RILOVIA 100/25 and RILOVIA 200/50** tablets, a mean 4,7-fold and 5,9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with **RILOVIA 100/25 and RILOVIA 200/50**, the lowest possible dose of atorvastatin should be administered. Results from an interaction study with **RILOVIA 100/25 and RILOVIA 200/50** tablets and pravastatin revealed no

clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4 and interactions are not expected with **RILOVIA 100/25 and RILOVIA 200/50**. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Glucocorticosteroids:

Fluticasone propionate (interaction with ritonavir):

In a clinical study where ritonavir 100 mg capsules twice daily were co-administered with 50 µg intranasal fluticasone propionate (4 times daily) for seven days in healthy subjects, the fluticasone propionate plasma levels increased significantly, whereas the intrinsic cortisol levels decreased by approximately 86 % (90 % confidence interval 82 − 89 %). Greater effects may be expected when fluticasone propionate is inhaled. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have 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. Consequently, concomitant administration of **RILOVIA 100/25 and RILOVIA 200/50** and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may have to be performed over a longer period. The effect of high fluticasone systemic exposure on ritonavir plasma levels is yet unknown.

Dexamethasone:

May induce CYP3A4 and may decrease lopinavir concentrations.

Phosphodiesterase inhibitors:

Phosphodiesterase inhibitors which are dependent on CYP3A4 metabolism, such as tadalafil and sildenafil, are expected to result in an approximately 2-fold and 11-fold increase in AUC respectively, when co-administered with ritonavir containing regimens including **RILOVIA 100/25 and RILOVIA 200/50** and may result in an increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. Particular caution must be used when

prescribing sildenafil or tadalafil in patients receiving **RILOVIA 100/25 and RILOVIA 200/50** with increased monitoring for adverse events. Doses of no more than 25 mg sildenafil every 48 hours and 10 mg tadalafil every 72 hours. Co-administration of vardenafil with ritonavir containing regimens including **RILOVIA 100/25 and RILOVIA 200/50** is expected to result in 49-fold increase in vardenafil AUC. The use of vardenafil with **RILOVIA 100/25 and RILOVIA 200/50** is contra-indicated.

Concomitant use of sildenafil with **RILOVIA 100/25 and RILOVIA 200/50** is contra-indicated in pulmonary arterial hypertension (PAH) patients.

Cyclosporin, sirolimus (rapamycin) and tacrolimus:

Concentrations may be increased when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilised.

Antifungals:

Ketoconazole and itraconazole:

May have serum concentrations increased by **RILOVIA 100/25 and RILOVIA 200/50**. High doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.

Voriconazole:

Due to the potential for reduced voriconazole concentrations, co-administration of voriconazole and ritonavir as contained in **RILOVIA 100/25 and RILOVIA 200/50** should be avoided unless an assessment of the benefit/risk to patient justifies the use of voriconazole.

Anti-infectives:

Clarithromycin:

Moderate increases in clarithromycin AUC are expected when co-administered with **RILOVIA 100/25 and RILOVIA 200/50**. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Methadone:

RILOVIA 100/25 and RILOVIA 200/50 tablets were demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Contraceptives:

Levels of ethinyl oestradiol were decreased when oestrogen-based oral contraceptives were co-administered with **RILOVIA 100/25 and RILOVIA 200/50** tablets. In case of co-administration of **RILOVIA 100/25 and RILOVIA 200/50** with contraceptives containing ethinyl oestradiol (whatever the contraceptive formulation e.g. oral or patch), alternative methods of contraception are to be used.

Antimycobacterials:

Rifabutin:

When rifabutin and **RILOVIA 100/25 and RILOVIA 200/50** tablets were co-administered for 10 days, rifabutin (parent substance and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3,5- and 5,7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or 3 times per week) is recommended when administered with **RILOVIA 100/25 and RILOVIA 200/50**. Further reduction of rifabutin dose may be necessary.

Rifampicin:

Co-administration of **RILOVIA 100/25 and RILOVIA 200/50** with rifampicin is not recommended. Rifampicin administered with **RILOVIA 100/25 and RILOVIA 200/50** caused large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect and possible resistance to **RILOVIA 100/25 and RILOVIA 200/50** or to the class of protease inhibitors or other co-administered antivirals. Therefore, this co-administration should be avoided unless judged strictly necessary. If this co-administration is judged unavoidable, increased dose of lopinavir /ritonavir tablets at 400 mg/400 mg twice daily may be administered with rifampicin under close safety and therapeutic monitoring. The lopinavir /ritonavir tablets dose should be titrated upward only after rifampicin has been initiated.
Close monitoring of liver function is indicated.

St John's Wort:

Serum levels of **RILOVIA 100/25 and RILOVIA 200/50** can be reduced with resultant loss of therapeutic effect and development of resistance by concomitant use of the herbal preparation St John's Wort (*Hypericum perforatum).* This is due to the induction of metabolising enzymes by St John's Wort. Herbal preparations containing St. John's Wort should therefore not be combined with **RILOVIA 100/25 and RILOVIA 200/50** (see **CONTRA-INDICATIONS**).

Acid reducing agents (omeprazole, ranitidine):

No clinically relevant interaction is expected when **RILOVIA 100/25 and RILOVIA 200/50** are co-administered with omeprazole or with ranitidine.

General:

Based on known metabolic profiles, clinically significant interactions are not expected between **RILOVIA 100/25 and RILOVIA 200/50** tablets and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.

PREGNANCY AND LACTATION:

There are no data from the use of **RILOVIA 100/25 and RILOVIA 200/50** in pregnant women. Studies in animals have shown reproductive toxicity. **RILOVIA 100/25 and RILOVIA 200/50** should not be used during pregnancy.

Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether **RILOVIA 100/25 and RILOVIA 200/50** are excreted in human milk. HIV infected women must not breast-feed their infants under any circumstances to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE:

RILOVIA 100/25 and RILOVIA 200/50 tablets should be prescribed by doctors who are experienced in the treatment of HIV infection.

RILOVIA 100/25 and RILOVIA 200/50 tablets should be swallowed whole and not chewed, broken or crushed.

RILOVIA DS (200 mg/50 mg)

Adult and adolescent use: The recommended dosage of **RILOVIA DS** is two 200/50 mg tablets twice daily taken with or without food.

RILOVIA (100 mg/25 mg)

Children less than 2 years of age: **RILOVIA 100/25 and RILOVIA 200/50** are not recommended for use in children below 2 years of age due to insufficient data on safety and efficacy.

Paediatric use (2 years of age and above): The adult dose of **RILOVIA 100/25 and RILOVIA 200/50** (400/100 mg twice daily) may be used in children 40 kg or greater or with a Body Surface Area (BSA)* greater than 1,4 m^2.

The following table contains dosing guidelines for **RILOVIA** (100/25 mg) tablets based on BSA.

Paediatric Dosing Guidelines	
Body Surface Area (m^2)	**Recommended number of RILOVIA (100/25 mg) tablets twice-daily**
≥ 1,4	4 tablets (400/100 mg)

* Body surface area can be calculated with the following equation:

BSA (m^2) = √ (Height (cm) X Weight (kg) / 3600)

Children less than 2 years of age: **RILOVIA 100/25 and RILOVIA 200/50** are not recommended for use in children below 2 years of age due to insufficient data on safety and efficacy.

Concomitant therapy: Efavirenz or nevirapine

The following table contains dosing guidelines for **RILOVIA 100/25 and RILOVIA 200/50** based on BSA when used in combination with efavirenz or nevirapine in children.

Paediatric Dosing Guidelines with concomitant efavirenz or nevirapine	
Body Surface Area (m^2)	**Recommended number of RILOVIA (100/25 mg) tablets twice-daily. The adequate dosing may be achieved with the two available strengths of lopinavir/ritonavir tablets: RILOVIA (100/25 mg) and RILOVIA DS (200/50 mg.)***
≥ 1,4	500/125 mg

* **RILOVIA 100/25 and RILOVIA 200/50** tablets must not be chewed, broken or crushed.

Hepatic impairment: In HIV-infected patients with mild to moderate hepatic impairment, an increase of approximately 30 % in lopinavir exposure has been observed. No data are available in patients with severe hepatic impairment.

RILOVIA 100/25 and RILOVIA 200/50 should not be given to these patients.

Renal impairment: No dose adjustment is necessary in patients with renal impairment. Caution is warranted when **RILOVIA 100/25 and RILOVIA 200/50** are used in patients with severe renal impairment.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The following side effects of moderate to severe intensity with possible or probable relationship to **RILOVIA 100/25 and RILOVIA 200/50** have been reported. The side effects are displayed by system organ class.

Undesirable Effects in Clinical Studies in Adult Patients		
Infections and infestations	Less frequent	Otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral

		infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Skin benign neoplasm, cyst
Blood and lymphatic system disorders	Less frequent	Anaemia, leucopenia and lymphadenopathy
Endocrine disorders	Less frequent	Hypogonadism male, Cushing syndrome, hypothyroidism
Metabolic and nutritional disorders	Less frequent	Avitaminosis, dehydration, oedema, increased appetite, lactic acidosis, obesity, anorexia, diabetes mellitus, hyperglycaemia, hypocholesterolaemia
Psychiatric disorders	Frequent	Insomnia
	Less frequent	Abnormal dreams, agitation, anxiety, confusion, depression, dyskinesia, emotional lability, decreased libido, nervousness, abnormal thinking
Nervous system disorders	Frequent	Headache, paraesthesia
	Less frequent	Dizziness, amnesia, ataxia, encephalopathy, facial paralysis, hypertonia, neuropathy, peripheral neuritis, somnolence, tremor, taste loss, taste perversion, migraine, extrapyramidal syndrome
Eye disorders	Less frequent	Abnormal vision, eye disorder
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Palpitation, lung oedema, myocardial infarction [1]
Vascular disorders	Less frequent	Hypertension, thrombophlebitis,

		vasculitis, varicose vein, deep thrombophlebitis, vascular disorder
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, rhinitis, increased cough
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, abdominal pain, abnormal stools, dyspepsia, flatulence, gastrointestinal disorder
	Less frequent	Enlarged abdomen, constipation, dry mouth, dysphagia, enterocolitis, eructation, oesophagitis, faecal incontinence, gastritis, gastroenteritis, haemorrhagic colitis, mouth ulcerations, pancreatitis , sialadenitis, stomatitis, ulcerative stomatitis, periodontitis
Hepato-biliary disorders	Less frequent	Cholecystitis, hepatitis, hepatomegaly, liver fatty deposit, liver tenderness
Skin and subcutaneous tissue disorders	Frequent	Rash, lipodystrophy, acne
	Less frequent	Alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, nail disorder, pruritus, seborrhoea, skin discolouration, skin ulcer, face oedema, sweating, skin striae
Musculoskeletal and connective tissue disorders	Less frequent	Arthralgia, arthrosis, myalgia, back pain, joint disorder
Renal and urinary disorders	Less frequent	Kidney calculus, urine abnormality, albuminuria, hypercalcinuria, nephritis, hyperuricaemia
Reproductive system and	Less frequent	Abnormal ejaculation, amenorrhoea,

breast disorders		breast enlargement, gynaecomastia, impotence, menorrhagia
General disorders and administration site conditions	Frequent	Asthenia, pain
	Less frequent	Chest pain, substernal chest pain, chills, fever, flu syndrome, malaise, peripheral oedema
Investigations	Frequent	Increased triglycerides, increased total cholesterol, increased GGT, increased glucose, increased amylase, increased AST, increased ALT, abnormal liver function tests
	Less frequent	Decreased glucose tolerance, weight gain, weight loss, increased bilirubin, hormone level altered, lab test abnormal

[1] This event had a fatal outcome.

Paediatric patients:

In children BSA > 1,4 m^2, the nature of the safety profile is similar to that seen in adults.

Undesirable Effects in Paediatric Patients		
Infections and infestations	Frequent	Viral infection
Nervous system disorders	Frequent	Taste perversion
Gastrointestinal disorders	Frequent	Constipation, vomiting, pancreatitis
Hepatobiliary disorders	Frequent	Hepatomegaly
Skin and subcutaneous tissue disorders	Frequent	Rash, dry skin

General disorders and administration site conditions	Frequent	Fever
Investigations	Frequent	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

The most common adverse reaction associated with **RILOVIA 100/25 and RILOVIA 200/50** therapy was diarrhoea and was generally of mild to moderate severity. Discontinuation due to adverse reactions was 4,5 % (naïve patients) and 9 % (experienced patients) over a 48 week period.

It is important to note that cases of pancreatitis have been reported in patients receiving **RILOVIA 100/25 and RILOVIA 200/50**, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during **RILOVIA 100/25 and RILOVIA 200/50** therapy.

Increased 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 redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (‘buffalo hump’).

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

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.

Post marketing experience:

Hepatitis, and rarely jaundice, have been reported in patients on lopinavir and ritonavir tablets therapy such as in **RILOVIA 100/25 and RILOVIA 200/50**, in the presence or absence of identifiable risk factors for hepatitis.

Stevens-Johnson syndrome and erythema multiforme have been reported.

Bradydysrhythmia has been reported.

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.

Special Precautions:

Renal disease:

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

Driving and using machinery:

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 **RILOVIA 100/25 and RILOVIA 200/50**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is limited human experience of overdose with **RILOVIA 100/25 and RILOVIA 200/50**.

There is no specific antidote for overdose with **RILOVIA 100/25 and RILOVIA 200/50**. Treatment of overdose with **RILOVIA 100/25 and RILOVIA 200/50** 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 **RILOVIA 100/25 and RILOVIA 200/50** are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

IDENTIFICATION:

RILOVIA 100/25: Light yellow to yellow coloured, round, biconvex, film-coated tablets, debossed with "M172" on one side and plain on other side.

RILOVIA 200/50: Light yellow to yellow coloured, film-coated ovaloid tablets debossed with "M124" on one side and plain on the other side.

PRESENTATION:

RILOVIA 100/25 film-coated tablets will be packed in High Density Polyethylene (HDPE) bottle (Pill jar) pack (marketable pack) with white opaque polypropylene (PP) tamper evident closure with inbuilt desiccant packed into a carton in pack size of 56's, 112's and 120's*.

RILOVIA 100/25 film-coated tablets will be packed in High Density Polyethylene (HDPE) bottle (Pill jar) pack (marketable pack) with white opaque polypropylene (PP) tamper evident closure with inbuilt desiccant in pack sizes of 56's, 112's and 120's*.

RILOVIA 200/50 film-coated tablets will be packed in high density polyethylene (HDPE) bottle (Pill jar) pack (marketable pack) with white opaque polypropylene (PP) tamper evident closure with inbuilt desiccant packed into a carton in pack size of 112's and 120's*.

RILOVIA 200/50 film-coated tablets will be packed in high density polyethylene (HDPE) bottle (Pill jar) pack (marketable pack) with white opaque polypropylene (PP) tamper evident closure with inbuilt desiccant in pack sizes of 112's and 120's*.

High density polyethylene (HDPE) bottle pack (marketable pack) comprising of white opaque HDPE bottle with white opaque polypropylene (PP) child resistant closure with aluminium induction sealing wad packed into a carton in pack size of 112's and 120's*. Separate desiccant is included in the final pack.

High density polyethylene (HDPE) bottle pack (marketable pack) comprising of white opaque HDPE bottle with white opaque polypropylene (PP) child resistant closure with aluminium induction sealing wad in pack sizes of 112's and 120's*.

*Not all packs may be marketed.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Store in the original container. Do not

Remove from the carton until required for use. Keep the bottles tightly closed.

KEEP THIS MEDICINE OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBERS:

RILOVIA 100/25: 45/20.2.8/0336

RILOVIA 200/50: 45/20.2.8/0111

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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