PROPOSED PROFESSIONAL INFORMATION FOR

PARANVIR 75/150/400/600 mg (film coated tablets)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PARANVIR 75 (Film coated tablets)

PARANVIR 150 (Film coated tablets)

PARANVIR 400 (Film coated tablets)

PARANVIR 600 (Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARANVIR 75

Each film coated tablet contains 75 mg of darunavir (as darunavir ethanolate).

PARANVIR 150

Each film coated tablet contains 150 mg of darunavir (as darunavir ethanolate).

PARANVIR 400

Each film coated tablet contains 400 mg of darunavir (as darunavir ethanolate).

PARANVIR 600

Each film coated tablet contains 600 mg of darunavir (as darunavir ethanolate).

Sugar free

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

PARANVIR 75

White to off-white, capsule shaped, biconvex film coated tablet debossed with 'DNV' on one side and '75' on other side.

PARANVIR 150

White to off white, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side and '150' on other side.

PARANVIR 400

Light orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side and '400' on other side.

PARANVIR 600

Orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side and '600' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARANVIR *400 mg*

PARANVIR, in combination with low dose ritonavir and with other antiretroviral medicines, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced adult patients who are protease-inhibitor-naive patients or after exclusion of darunavir resistance associated mutations (DRV-RAMs· V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V). Ritonavir is used as a pharmacokinetic enhancer of darunavir.

PARANVIR *600 mg*

PARANVIR, in combination with 100 mg ritonavir and with other antiretroviral medicines, is indicated for the treatment of HIV infection in antiretroviral treatment experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

This indication is based on a 24 week study consisting of treatment-experienced, HIV-1-infected patients where the combination of **PARANVIR** and ritonavir indicated a greater reduction of plasma HIV RNA levels and greater increase in CD4+ cell counts when compared to a protease inhibitor regimen of choice, each given in combination with other antiretrovirals.

There is no information on the use of **PARANVIR** in antiretroviral treatment-naïve adult patients.

PARANVIR *75/150 mg*

Paediatric patients

PARANVIR, in combination with low dose ritonavir and with other antiretroviral medicines, is indicated for the treatment of HIV-infection in antiretroviral treatment-experienced paediatric patients of six years to < 18 years.

There is no information on the use of darunavir in combination with ritonavir in the paediatric population for the once daily dose.

Treatment history, and when available, genotypic or phenotypic testing, should guide the use of **PARANVIR.**

4.2 Posology and method of administration

Posology

PARANVIR must always be given with low-dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicines. The prescribing information of ritonavir must therefore be consulted prior to initiation of therapy with **PARANVIR**. After therapy with **PARANVIR** has been initiated, patients should be advised not to alter the dosage or discontinue therapy without instruction of their medical practitioner.

PARANVIR *400 mg*

PARANVIR/ ritonavir 800/100 mg once daily dosing regimen is recommended in HIV protease – inhibitor naïve patients and in treatment-experienced patients with demonstrated absence of DRV-RAMs.

Children (less than 12 years of age) and adolescents (12 to 17 years of age):

The safety and efficacy of the once daily dose of **PARANVIR**/ rtv (ritonavir) in paediatric patients has not been established.

PARANVIR *600 mg*

Adults:

The recommended dosage of **PARANVIR** is one 600 mg tablet twice daily taken with ritonavir 100 mg twice daily and with food.

A further increase in the dose of **PARANVIR** or ritonavir has been shown not to result in any clinically relevant increase in antiviral activity.

Children (less than 12 years of age) and adolescents (12 to 17 years of age):

The safety and efficacy of **PARANVIR**/ rtv in these populations are not known.

PARANVIR *75/150 mg*

Antiretroviral treatment-experienced paediatric patients (six to< 18 years of age)

The recommended dose of **PARANVIR** for paediatric patients (six to < 18 years of age and weighing at least 20 kg) is based on body weight (see the table below) and should not exceed the recommended adult dose (600 mg/ 100 mg) twice daily). **PARANVIR** tablets should be taken with ritonavir twice daily.

Recommended dosed for treatment-experienced paediatric patients (six to < 18 years of age for PARANVIR tablets and ritonavir	
Body weight (kg)	**Dose**
≥ 20 kg - < 30 kg	375 mg **PARANVIR**/50 mg ritonavir twice daily
≥ 30 kg - < 40 kg	450 mg **PARANVIR**/60 mg ritonavir twice daily
≥ 40 kg	600 mg **PARANVIR**/100 mg ritonavir twice daily

Children (less than 12 years of age) and adolescents (12 to 17 years of age):

The safety and efficacy of **PARANVIR**/ rtv in these populations are not known.

There is no information on the use of darunavir in combination with ritonavir in the paediatric population for a once daily dose.

Antiretroviral treatment-experienced children < 6 years of age and antiretroviral treatment-naïve paediatric patients:

The safely and efficacy of **PARANVIR** in antiretroviral treatment-experienced children aged (three) 3 to < 6 years and in all antiretroviral treatment- naïve paediatric patients

have not been established. **PARANVIR**/ rtv should not be used in children below (three) 3 years of age.

PARANVIR 75/150/400/600

Special populations:

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of **PARANVIR** when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. **PARANVIR** should not be used in patients with severe hepatic impairment, as safety and efficacy have not been demonstrated (see **section 4.4**).

Renal impairment

No dose adjustment is required in patients with renal impairment (see **section 4.4** and **section 5.2**).

Elderly

Limited information is available in this population, and therefore **PARANVIR** should be used with caution in this age group (see section 4.4 and 5.2)

Method of administration

Patients should be advised to take **PARANVIR** with food every day as prescribed. The type of food does not affect the exposure to darunavir. Ritonavir is used as a pharmacokinetic enhancer of darunavir

Patient should be instructed to swallow whole tablets with a drink such as water or milk. In case a dose of **PARANVIR** and/ or ritonavir was missed within 12 hours (for a

once a day dose) or 6 hours (for a twice a day dose) of the time it is usually taken, patients should be instructed to take the prescribed dose of **PARANVIR** and ritonavir with food as soon as possible. If this was noticed later than 6 hours (twice a day dose) or 12 hours (once a day dose) after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

4.3 Contraindications

- Hypersensitivity to darunavir or to any of the excipients of **PARANVIR** (see **section 6.1).**
- Children below the age of three years (see **section 4.4**).
- Patients with severe (Child – Pugh Class C) hepatic impairment.
- The presence of a contraindication to ritonavir.
- Co-administration with the combination product lopinavir/ ritonavir.
- Co-administration with quetiapine as it may increase quetiapine -related toxicity and/ or coma.
- Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A4 (CYP3A4) isoform. **PARANVIR**/rtv should not be co-administered with medicines that are highly dependent on CYP3A4 for clearance and for which increased plasma concentrations are associated with serious and/ or life-threatening events (narrow therapeutic index).

Medicines that are contraindicated with **PARANVIR**/rtv are listed below (see **section 4.5**):

- Inducers of CYP450 metabolism for example carbamazepine, phenobarbitone and phenytoin,
- Antimycobacterial for example rifampicin and rifabutin,
- PDE-5 inhibitors for example sildenafil, when used to treat pulmonary arterial hypertension (see **section 4.5**),
- Alpha 1-adenoreceptor antagonist for example alfuzosin,
- Ergot derivatives for example dihydroergotamine, ergonovine, ergotamine and methyergonovine,
- Herbal products such as St. John's Wort (*Hypericum perforatum*),
- 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitors for example lovastatin and simvastatin,
- Neuroleptic medicines such as pimozide,
- Sedatives/hypnotics for example midazolam and triazolam,
- Antifungals for example ketoconazole, itraconazole and voriconazole,
- Buprenorphine or naloxone,
- Amiodarone,
- Colchicine when used in patients with renal/ and or hepatic impairment,
- Cisapride,
- Dabigatran, ticagrelor,
- Antihistamines for example astemizole,
- Endothelin receptor antagonist such as bosentan,
- Hepatitis C virus (HCV) direct-acting antivirals: NS3-4A protease inhibitors such as boceprevir and telaprevir.

4.4 Special warnings and precautions for use

PARANVIR should not be used in patients with severe hepatic impairment (see **section 4.2**).

PARANVIR must be co-administered with ritonavir and food to exert its therapeutic effect (see **section 4.2**). Failure to correctly administer **PARANVIR** with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect. Please refer to ritonavir prescribing information for additional information on precautionary measures.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/ accumulation of body fat, including central obesity, dorsa-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome:

Immune Reconstitution Inflammatory Syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune response to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting Combination Anti-Retroviral Therapy (cART). Typically, such reaction presents

by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Grave's disease and autoimmune haemolytic anaemia) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections:

Patients receiving **PARANVIR** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including **PARANVIR**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Skin rash:

During the clinical development program, severe skin reactions, which may be accompanied with fever and/or elevation of transaminases has been reported. Stevens-Johnson Syndrome has been reported; and during post-marketing experience toxic epidermal necrolysis has been also reported. Discontinue **PARANVIR** immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and or eosinophilia. Rash (all grades, regardless of causality) occurred in 10,3 % of patients treated with darunavir. The discontinuation rate due to rash in patients using darunavir such as in **PARANVIR**/rtv was 0,5 %.

Rash occurred more frequently in treatment-experienced regimens containing-darunavir/rtv + raltegravir compared to subjects receiving darunavir/rtv without raltegravir or raltegravir without darunavir/rtv. However, rash that was considered treatment-related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy.

Sulphur allergy:

Darunavir contains a sulphonamide moiety. **PARANVIR** should be used with caution in patients with a known sulphonamide allergy.

Diabetes mellitus/ Hyperglycaemia:

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported in HIV-infected patients receiving darunavir such as in **PARANVIR**.

Other precautions:

PARANVIR should not be used in children below three years of age in view of toxicity observed in juvenile rat's dose with darunavir (from 20 mg/kg to 1, 000 mg/kg) (see **section 4.3**)

The safety and efficacy of **PARANVIR** in antiretroviral treatment-experienced children aged three to < 6 years and in antiretroviral treatment-naïve paediatric patients have not been established.

Elderly:

As limited information is available on the use of **PARANVIR** in patients age 65 and over caution should be exercised in the administration of **PARANVIR** in elderly patients, reflecting the greater frequency of decreased hepatic function and concomitant disease or other therapy (see **section 5.2**).

Patients with co-existing conditions:

Hepatic impairment

There are no data regarding the use **PARANVIR** when co-administered to patients with severe hepatic impairment; therefore, **PARANVIR** should not be used. No dose adjustment is required in patients with mild to moderate hepatic impairment (see **section 4.2** and **section 5.2**).

Hepatotoxicity

Medicine induced hepatitis (e.g. acute hepatitis, cytolitic hepatitis) has been reported with **PARANVIR**.

Patients with pre-existing liver dysfunctions, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events. Appropriate laboratory testing should be conducted prior to initiating therapy with **PARANVIR** and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevation of transaminases, and especially during the first several months of

PARANVIR treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly) in patients on **PARANVIR** should prompt consideration of interruption or discontinuation of **PARANVIR** treatment.

Renal impairment

Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see **section 4.2** and **section 5.2**).

Haemophilia patients

There have been reports of increase bleedings, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with PIs such as **PARANVIR**. Haemophilia patients should therefore be made aware of the possibility of increased bleeding.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style.

Medicine interactions

Darunavir and ritonavir are both inhibitors of the CYP3A isoenzyme. Co-administration of **PARANVIR** and ritonavir with medicines primarily metabolised by CYP3A may result in increased plasma concentration of such medicines, which could increase or prolong their therapeutic effect and adverse events (see **section 4.3** and **section 4.5**).

For medicines that are highly dependent on metabolism by CYP3A and that have a narrow therapeutic index, such as amiodarone, bepridil (systemic) lidocaine and quinidine, plasma concentrations of such medicines could increase when combined with **PARANVIR**/rtv. This can lead to prolongation or increase of their therapeutic effect and adverse events (see **section 4.5**).

The HMG-CoA reductase inhibitors (statins) simvastatin and lovastatin are highly dependent of CYP3A for their metabolism. Concomitant use of **PARANVIR** with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy, including rhabdomyolysis, as a consequence of increased plasma concentration of simvastatin or lovastatin. Darunavir increased exposure to pravastatin by up to 80 %. The clinical relevance of this interaction is unknown. It is not recommended to co-administer pravastatin with **PARANVIR**. If treatment with atorvastatin is indicated with **PARANVIR,** reduced starting doses of atorvastatin are recommended (see **section 4.5**).

Oestrogen-based contraceptives:

Plasma concentrations of ethinylestradiol are decreased by induction of its metabolism by ritonavir and alternative methods of non-hormonal contraception are recommended (see section 4.5).

PDE-5 inhibitors

The phosphodiesterase type five (PDE-5) inhibitors sildenafil, vardenafil and tadalafil are highly dependent on CYP3A for their metabolism. If concomitant use of PARANVIR with sildenafil, vardenafil or tadalafil is indicated for other uses than pulmonary arterial hypertension, reduced doses of the PDE-5 inhibitors are recommended (see section 4.5).

Colchicine

Life - threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein.

4.5 Interaction with other medicines and other forms of interaction

Darunavir and ritonavir are both inhibitors of the cytochrome P450 CYP3A isoenzyme. Co-administration of **PARANVIR** and ritonavir and medicines primarily metabolised by CYP3A may result in increased plasma concentrations of such medicines, which could increase or prolong their therapeutic effect and adverse events. **PARANVIR**/rtv should not be co –administered with medicines that are highly dependent of CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life- threatening events (narrow therapeutic index).

These medicines include carbamazepine, phenobarbitone and phenytoin, astemizole rifampicin, St. John's Wort (*Hypericum perforatum*), simvastatin, lovastatin, antifungals (ketoconazole, itraconazole and voriconazole), buprenorphine, naloxone alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), midazolam, triazolam, pimozide and the ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine) (see **section 4.3**).

Rifampicin is a potent inducer of CYP450 metabolism. **PARANVIR** ~~should not be used~~ in combination with rifampicin is contraindicated as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect of **PARANVIR** (see **section 4.3**).

PARANVIR/rtv should not be used concomitantly with products containing St. John's Wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations (see **section 4.3** and **section 4.4**).

Antiretroviral medicines

Nucleoside/nucleotide reverse transcriptase inhibitors (N(t) RTIs)

Didanosine

PARANVIR in combination with ritonavir (600/100 mg twice daily) did not significantly affect didanosine exposure. The combination **PARANVIR** co-administered with low dose ritonavir and didanosine can be used without dose adjustments. As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered one hour before or two hours after **PARANVIR** (which is administered with food).

Tenofovir

The results of an interaction study with tenofovir (tenofovir disoproxil fumarate 300 mg once daily) demonstrated that the systemic exposure of tenofovir was increased by 22 % when co-administered with darunavir (300/100 mg twice daily). This finding is not considered to be clinically relevant. There was no change in the urinary excretion of tenofovir or darunavir during concomitant administration. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustment of **PARANVIR** or tenofovir disoproxil fumarate are required when these medicines are co-administered.

Other NRTIs

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabline, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no interactions are expected for these medicines and **PARANVIR** combined with ritonavir.

Non-nucleoside reverse transcriptase inhibitors (NNTRIs)

Etravirine

In an interaction trial between darunavir combined with ritonavir (600/100 mg twice daily) and etravirine, there was a 37 % decrease in etravirine exposure and no relevant change in exposure to darunavir. Therefore, **PARANVIR** can be co-administered with etravirine 200 mg twice daily without adjustments.

Efavirenz

An interaction study with darunavir in combination with ritonavir (300/100 mg twice daily) and efavirenz (600 mg once daily) has been performed. In the presence of efavirenz, a decrease of 13 % for darunavir exposure and a decrease of darunavir C_{min} by 31 % were observed. Exposure to efavirenz was increased by 21 % when administered in combination with darunavir and ritonavir. The combination of darunavir and efavirenz should be used with caution.

Nevirapine

The results of an interaction study with darunavir and ritonavir (400/100 mg twice daily and nevirapine (200 mg twice daily) demonstrated that darunavir exposure was not affected when administered concomitantly with nevirapine. Exposure to nevirapine increased by 27 % (compared to historical controls) when administered in combination with darunavir and ritonavir. Since this difference is not considered to be clinically relevant, the combination of **PARANVIR** and ritonavir and nevirapine can be used without dose adjustments.

Rilpivirine

In an interaction trial between darunavir and ritonavir (800/100 mg daily) and rilpivirine (150 mg daily) no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130 % (2,3-fold) when administered in combination with darunavir. Since this difference is not considered to be clinically relevant, the combination of **PARANVIR** and ritonavir and rilpivirine can be used

without dose adjustments.

HIV protease inhibitors (PIs)

Ritonavir

The overall pharmacokinetics enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg **PARANVIR** was given orally in combination with ritonavir at 100 mg twice daily. Therefore, **PARANVIR** should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see **section 4.4** and **section 5.2**).

Lopinavir/ritonavir

Results of interaction studies with darunavir with or without ritonavir and lopinavir/ritonavir demonstrated a decrease in the exposure (AUC) of darunavir by 40 %. The appropriate dose of the combination has not been established. Hence, it is not recommended to co-administer **PARANVIR** with lopinavir/ritonavir.

Saquinavir

In an interaction study between darunavir (400 mg twice daily), saquinavir (1 000 mg twice daily) and ritonavir (100 mg twice daily), darunavir exposure was decreased by 26 % in the presence of saquinavir; saquinavir exposure was not affected by the presence of **PARANVIR**. It is not recommended to combine saquinavir and **PARANVIR**.

Atazanavir

It has been reported that co-administration of darunavir in combination with ritonavir and atazanavir in combination with ritonavir does not significantly affect systemic exposure of both darunavir and atazanavir. Atazanavir can be co-administered with **PARANVIR**.

Indinavir

In an interaction study between darunavir in combination with ritonavir (400/100) twice daily and indinavir (800 mg twice daily), darunavir exposure was increased by 24 % in the presence of indinavir; indinavir exposure was increased by 23 % in the presence of darunavir.

Other HIV protease inhibitor

The co-administration of **PARANVIR** and PIs other than lopinavir/ritonavir, saquinavir, atazanavir and indinavir have not been studied. Therefore, such co-administration is not recommended.

Other medicines

CCR5 antagonist

When used in combination with **PARANVIR** and ritonavir, the dose of maraviroc should be 150 mg twice daily.

Alpha 1-adrenoreceptor antagonist (Alfuzosin)

There is a potential for serious and/or life-threatening reactions such as hypotension. Concomitant use with **PARANVIR** is contraindicated.

Antidysrhythmic medicines (bepridil, lidocaine, quinidine and amiodarone) **(2: J3)**

Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with **PARANVIR**. Caution is warranted and therapeutic monitoring of antidysrhythmic medicines, is recommended, when co-administered with **PARANVIR**.

Digoxin

An interaction trial with darunavir in combination with ritonavir (600/100 mg twice daily) and a single dose of digoxin (0,4 mg) showed an increase of digoxin AUC last of 77 % (ratio of least square means (LSM) was 1, 77 with a 90 % CI of 0,90 to 3,50). It is recommended that the lowest dose of digoxin should initially be prescribed, and digoxin dose should be titrated to obtain the desired clinical effect when co-administered with **PARANVIR**. Serum digoxin concentrations should be monitored to assist in the titration.

Anticoagulants

Warfarin concentrations may be affected (decreased) when co-administered with **PARANVIR**. It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with **PARANVIR**.

The use of **PARANVIR** co-administered with low dose ritonavir and anticoagulants such as apixaban and rivaroxaban are not recommended.

Anticonvulsant medicines (phenobarbitone, phenytoin)

Phenobarbitone and phenytoin are inducers of CYP450 enzymes.

PARANVIR should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **PARANVIR (**see **section 4.3** and **section 4.4).** Clinical monitoring is required if **PARANVIR** is used with Clonazepam as the concentration of clonazepam may increase.

Carbamazepine

An interaction trial between darunavir in combination with ritonavir (600/ 100 mg twice daily) and carbamazepine (200 mg twice daily) showed that the exposure to darunavir co- administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC_{12h}) was decreased by 49 %. The carbamazepine, AUC_{12h} was increased by 45 %. No dose adjustment for **PARANVIR**/rtv is recommended (see **section 4.3**).

Colchicine

Concomitant use of colchicine and **PARANVIR** may increase the exposure to colchicine. Patients with renal or hepatic impairment should not be given colchicine in combination with **PARANVIR**.

Calcium channel blockers

The exposure to calcium channel blockers (e.g. felodipine, nifedipine, nicardipine, amlodipine, diltiazem, verapamil) may increase when **PARANVIR** is used concomitantly. Caution is warranted and careful clinical monitoring is recommended.

Rifampicin

Rifampicin is a potent inducer of the CYP450 metabolism. **PARANVIR** should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to **PARANVIR**.

Clarithromycin

An interaction study between darunavir in combination with ritonavir (twice daily) and clarithromycin (500 mg twice daily) showed an increase in exposure to clarithromycin by 57 % while exposure to darunavir was not affected. For patients with renal impairment, a dose reduction of clarithromycin should be considered. No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustment should be considered.

- For patients with CLcr of 30 - 60 mL/min, the dose of clarithromycin should be reduced by 50 %.
- For patients with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75 %.

Dexamethasone

Dexamethasone induces CYP3A and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect. Therefore, this combination should be used with caution.

Bosentan

Concomitant use of bosentan and **PARANVIR** may increase plasma concentration of bosentan.

Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)

Contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues (see **section 4.3**).

Inhaled corticosteroids

Concomitant use of inhaled corticosteroids such as fluticasone, betamethasone, budesonide, mometasone, prednisone or triamcinolone and **PARANVIR** increases the plasma concentrations of these corticosteroids. Alternatives which are less dependant on CYP3A metabolism should be considered particularly for long-term use such as beclomethasone for intranasal or inhalation use.

Hepatitis C Virus (HCV) direct-acting antiviral medicines

NS3-4A inhibitors

Bocepravir

In an interaction study between **PARANVIR**/ rtv (600/ 100mg bid) and bocepravir (800mg three limes daily), darunavir exposure was reduced by 44 % and boceprevir exposure was reduced by 32 %. It is not recommended to co-administer **PARANVIR**/rtv with boceprevir (See **section 4.3**).

Taleprevir

In an interaction study between **PARANVIR** in combination with ritonavir (600/100 mg twice daily) and taleprevir (750 mg every eight hours), darunavir exposure was reduced by 40 % and taleprevir exposure was reduced by 35 %. It is not recommended that **PARANVIR** be co-administered with taleprevir.

HMG-CoA reductase inhibitors

The plasma concentrations of HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are markedly increased when co-administered with **PARANVIR**. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of **PARANVIR** with lovastatin and simvastatin is therefore contraindicated (see **section 4.3**). The results of an interaction study with atorvastatin (10 mg once daily) in combination with darunavir resulted in an exposure of atorvastatin that was 15 % lower than that obtained with atorvastatin alone. When co-administration of atorvastatin and **PARANVIR** is desired, it is recommended to start

with an atorvastatin dose of 10 mg once daily. A gradual dose increase of atorvastatin may be tailored to the clinical response.

Darunavir increased exposure to a single dose of pravastatin (40 mg) by up to 80 %. It is therefore not recommended to co-administer pravastatin with **PARANVIR**.

When **PARANVIR** is administered with rosuvastatin, it is recommended to start with the lowest possible dose of rosuvastatin and titrate to the desired clinical effect while monitoring safety.

H2 histamine-receptor antagonists and proton pump inhibitors

Co-administration of omeprazole (20 mg once daily) or ranitidine (150 mg twice daily) and **PARANVIR** did not affect the exposure to darunavir.

Inhaled beta agonist (salmeterol)

Concomitant use of salmeterol and **PARANVIR** is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitation and sinus tachycardia.

Immunosuppressant medicines (ciclosporin, tacrolimus, sirolimus)

Exposure to ciclosporin, tacrolimus, and sirolimus may be increased when co-administered with **PARANVIR**. Therapeutic drug monitoring of the immunosuppressive medicine is recommended when co-administered with **PARANVIR**.

Ketoconazole, itraconazole and voriconazole

Ketoconazole, itraconazole and voriconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole or voriconazole and **PARANVIR** may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by **PARANVIR**. The concomitant administration of ketoconazole (200 mg twice daily) with darunavir increased exposure of ketoconazole and darunavir by 212% and 42 % respectively. Concomitant use of ketoconazole, itraconazole and voriconazole with **PARANVIR** is contraindicated (see **section 4.3**).

Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving **PARANVIR** (see **section 4.3**).

Antimalarials

An interaction study investigating the effect of darunavir in combination with artemether and lumefantrine showed the AUC for artemether decrease by 16 % and increase by 175 % for lumefantrine. The use of **PARANVIR** with artemether/ lumefantrine can be used without dose adjustments. However, due to the increase in lumefantrine exposure, the combination should be used with caution.

Methadone

An interaction study investigating the effect of darunavir in combination with ritonavir

(600/100 mg twice daily) on stable methadone maintenance therapy showed an AUC decrease of 16 % for R-methadone. Based on pharmacokinetic and clinical finding, no adjustment of methadone dosage is required when initiating co-administration of **PARANVIR**. However, clinical monitoring which is recommended as maintenance therapy may need to be adjusted in some patients (see **section 4.4**).

Buprenorphine/naloxone

The results of an interaction study with darunavir and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with **PARANVIR**. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring Is recommended if **PARANVIR** and buprenorphine are co-administered (see **section 4.3**).

Fentanyl, oxycodone, tramadol

Based on theoretical considerations co-administration of fentanyl, oxycodone, tramadol with **PARANVIR** and low dose ritonavir may increase plasma concentrations of these analgesics. Clinical monitoring is required.

Sedatives/Hypnotics (midazolam, triazolam)

Clinical monitoring is recommended if co-administering **PARANVIR** with other sedatives/ hypnotics such as buspirone, clorazepate, diazepam, flurazepam or zolpidem and a low dose of the sedative/ hypnotic should be considered.

Oestrogen-based contraceptives

The results of an interaction study between **PARANVIR** in combination with ritonavir (600/100 mg twice daily) and ethinylestradiol 35 mcg and norethindrone 1 mg demonstrated that at steady-stated systemic exposures to ethinylestradiol and norethindrone are decreased by 44 % and 14 %, respectively. Therefore, alternative methods of non-hormonal contraception should be used (see **section 4.4**).

If **PARANVIR** is co-administered with drospirenone containing products, clinical monitoring is required due to the potential for hyperkalaemia.

Progestogens

Ritonavir-boosted protease inhibitors as in the case of **PARANVIR** may reduce the efficacy of progestogens. Therefore, alternative methods of contraception should be used.

PDE-5 inhibitors

Treatment of erectile dysfunction

In an interaction study a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir. Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with **PARANVIR**/rtv should be used with caution. If concomitant use of **PARANVIR**/rtv with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at single dose not exceeding

2,5 mg in 72 hours or tadalafil at a single dose not exceeding 10 mg in 72 hours is recommended (see **section 4.4**).

Treatment of pulmonary arterial hypertension

A safe and effective dose of sildenafil in combination with **PARANVIR** for treatment of pulmonary arterial hypertension has not been established. There is an increased potential for sildenafil-associated adverse events (including visual disturbances, hypotension prolonged erection and syncope). Therefore, co-administration of **PARANVIR** with sildenafil for pulmonary arterial hypertension is contraindicated (see **section 4.3**). For the treatment of pulmonary arterial hypertension with tadalafil co-administered with **PARANVIR**, dose adjustment for tadalafil is warranted. In patients who have been receiving **PARANVIR** for at least one week, tadalafil should be started at 20 mg every day, and increased to 40 mg every day, based upon individual tolerability. For patients on tadalafil and initiating **PARANVIR**, the use of tadalafil should be discontinued at least 24 hours prior to initiating **PARANVIR** and the use of tadalafil during the initiation of **PARANVIR** should be avoided.

After at least one week following the initiation of **PARANVIR**, tadalafil at 20 mg every day should be resumed, and increased to 40 mg every day, based upon individual tolerability.

Neuroleptic medicines

Pimozide is contraindicated in combination with **PARANVIR** due to the potential for serious and/or life-threatening reactions such as cardiac dysrhythmias (see **section 4.3**).

Rifabutin

Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure to darunavir by 57 % was observed, when darunavir in combination with ritonavir (600/100 mg twice daily) was administered with rifabutin (150 mg once every other day). Based on the safety profile of **PARANVIR**, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for **PARANVIR**/rtv. The exposure of rifabutin (the sum of rifabutin and its active metabolite) was increased 3-fold and the incidence of side effects was doubled (see section 4.3).

Selective Serotonin Reuptake Inhibitors (SSRIs)

In an interaction study between paroxetine (20 mg once daily) or sertraline (50 mg once daily) and darunavir, the exposure to darunavir was not affected by the presence of sertraline or paroxetine. Exposure to sertraline and paroxetine was decreased by 49 % and 39 % respectively in the presence of darunavir. If SSRIs are co-administered with **PARANVIR**, the recommended approached is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with **PARANVIR** should be monitored for antidepressant response.

St. John's wort (Hypericum perforatum)

PARANVIR should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum*) because co-administration may cause significant decrease in darunavir plasma concentrations. This may result in loss of therapeutic effect to **PARANVIR** (see **section 4.3**).

Antidepressants (Trazodone)

Concomitant use of trazodone and **PARANVIR** may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as darunavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Clinical monitoring is recommended if **PARANVIR** is co-administered with low dose ritonavir and antidepressants such as amitriptyline, desipramine, imipramine or nortriptyline. Adjustment of the antidepressant may be required.

Antipsychotics

Concomitant use of risperidone and **PARANVIR** may increase plasma concentrations of risperidone. Careful monitoring and a dose decrease may be required.

Antineoplastics

The concentrations of dasatinib, nilotinib, vinblastine or vincristine may increase when co-administered with **PARANVIR** and low dose ritonavir. Caution should be exercised. Concomitant use of everolimus and **PARANVIR** with low dose ritonavir is not recommended.

β – *Blockers*

Clinical monitoring is recommended when co-administering **PARANVIR** with β - blockers such as carvedilol, metoprolol or timolol as their plasma concentrations may increase.

4.6 Fertility, pregnancy and lactation

PARANVIR has not been studied in human pregnancy and lactation.

Pregnancy

Safety has not been demonstrated. In animal studies the exposure was lower than in human exposure, and no conclusions were possible.

Lactation

It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed their infants if they are receiving **PARANVIR**.

Fertility

No human data on the effect of darunavir on fertility are available. It has been reported that there was no effect on mating or fertility with darunavir treatment in rats.

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with regimens containing **PARANVIR**. This should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse events have been reported:

Infections and infestations

Less frequent: Herpes simplex

Blood and lymphatic system disorders

Less frequent: thrombocytopenia, neutropenia, anaemia, leukopenia, increased eosinophil count

Immune system disorder

Less frequent: immune reconstitution syndrome; hypersensitivity reactions, angioedema

Endocrine disorders

Less frequent: hypothyroidism, increased blood thyroid stimulating hormone

Metabolism and Nutrition disorders

Frequent: Diabetes mellitus, anorexia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia

Less frequent: Gout, decreased appetite, decreased weight, increased weight, insulin resistance, hyperglycaemia, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase, increased pancreatic lipase and amylase values, dyslipidemia, lipodystrophy, low density lipoprotein increased.

Psychiatric disorders

Frequent: Insomnia

Less frequent: Abnormal dreams, depression, disorientation, anxiety, sleep disorder, nightmare, decreased libido, confusional state, altered mood, restlessness

Nervous system disorders

Frequent: Headache, peripheral neuropathy, dizziness

Less frequent: lethargy, somnolence, hypoaesthesia, paraesthesia, dysgeusia, disturbance in attention, memory impairment, syncope, convulsion, ageusia, sleep phase rhythm disturbance

Eye disorders

Less frequent: Conjunctival hyperaemia, dry eye, visual disturbance

Ear and labyrinth disorders

Less frequent: Vertigo

Cardiac disorders

Less frequent: Myocardial infarction, tachycardia, transient ischaemic attacks, angina pectoris, prolonged electrocardiogram QT, sinus bradycardia, palpitations

Vascular disorders

Less frequent: hypertension, flushing

Respiratory, thoracic and mediastinal disorders

Less frequent: Nasopharyngitis, dyspnea, cough, epistaxis, throat irritation, rhinorrhea

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, abdominal pain, vomiting, dyspepsia, abdominal distension, flatulence, increased blood amylase

Less frequent: Acute pancreatitis, gastritis, gastroesophageal reflux disease,

aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia, stomatitis, haematemesis, cheilitis, dry lip, coated tongue, pancreatic enzymes increased

Hepatobiliary disorders

Frequent: Increased alanine aminotransferase

Less frequent: Acute hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, abnormal liver and pancreatic function tests, raised liver enzymes (alanine transaminase (ALT) aspartate transaminase (AST), alkaline phosphatase (ALP), increased blood bilirubin, increased gamma - glutamyltransferase)

Skin and subcutaneous tissue disorders

Frequent: Rash (including macular, aculopapular, papular, erythematous and pruritic rash), pruritus, lipodystrophy (lipohypertrophy, lipodystrophy and lipoatrophy)

Less frequent: Generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-

Johnson syndrome, erythema multiforme, dermatitis, skin lesion, xeroderma, folliculitis.

Unknown frequency: Toxic epidermal necrolysis, acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Frequent: Myalgia

Less frequent: Osteopenia, osteoporosis, osteonecrosis, increased blood creatine phosphokinase, muscle spasms, muscular weakness, arthralgia, pain in extremity, musculoskeletal stiffness, arthritis, joint stiffness, myositis, rhabdomyolysis

Renal and urinary disorders

Less frequent: Polyuria, nephrolithiasis, acute renal failure, renal failure, increased blood creatine, bilirubinuria, dysuria, nocturia, pollakiuria, proteinuria, decreased creatine renal clearance

Reproductive system and breast disorders

Frequent: Gynaecomastia

Less frequent: Erectile dysfunction

General disorders and administration site conditions

Frequent: Fatigue, asthenia

Less frequent: Pyrexia, chest pain, peripheral odema, malaise, feeling hot, irritability, pain, chills, abnormal feelings, xerosis

Paediatric population:

It was observed that the frequency, type and severity of adverse drug reactions in children and adolescents were similar to those in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions by e-mail: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free). In addition report any suspected adverse reactions to SAHPRA via “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Experience of overdose with **PARANVIR**/rtv is limited. There is not specific antidote for overdose with **PARANVIR**. Treatment of overdose with **PARANVIR** consists of general supportive and symptomatic treatment measures. Administration of activated

charcoal may be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral medicines, ATC code: J05AE10

Mechanism of action

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-encoded Gag-Pol polyproteins in virus-infected cells thereby preventing the formation of mature infectious virus particles.

Darunavir binds tightly to the HIV-1 protease.

Antiviral activity in vitro

Darunavir exhibited activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, humans peripheral blood mononuclear cells and human monocytes/macrophages *in-vitro* with median EC_{50} values ranging from 1,2 to 8,5 nM (0,7 to 5,0 ng/mL).

Resistance in vitro

In-vitro darunavir-resistant virus isolates from wild type HIV-1 were selected.

Viruses showing decreased susceptibility to darunavir (range: 6 - 21-fold)

harboured three to six amino acid substitution in protease gene.
Determinants of decreased susceptibility to darunavir in those viruses have not been identified.
In-vitro selection of darunavir-resistant HIV-1 (range: 53-641-fold change in EC_{50} values) from nine HIV-1 strains harbouring multiple PI (protease inhibitor) resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, 147V, 150V, L63P, A71Vand I84V were present in more than 50 % of the nine darunavir-resistant isolates. A minimum of eight of these darunavir *in-vitro* selected mutations, at least two which were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold-change [FC] > 1 0) to darunavir.
In 1113 clinical isolates resistant to at least one protease inhibitor and in 886 baseline isolates from the patients enrolled in the clinical trials only subgroups with > 10 PI resistance associated mutations showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among HIV protease inhibitors. Darunavir has a < 10 - fold decreased susceptibility against 90 % of 3 309 clinical isolates resistance to at least one protease inhibitor. Cross resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitor, the non-nucleoside reverse transcriptase inhibitors of the fusion inhibitors, is

unlikely because the viral targets for those inhibitors are different.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of alpha 1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding the plasma AAG and therefore, higher plasma concentrations. Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentration of darunavir considerably.

Absorption:

Darunavir is absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2,5 - 4,0 hours. The absolute oral bioavailability of single 600 mg dose of darunavir alone is approximately 37 % and increased to approximately 82 % in the presence of 100 mg twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir is approximate 14-fold increase in the system exposure of darunavir when single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see **section 4.4**).

When administered without food, the relative bioavailability of darunavir in the presence of low-dose ritonavir is 30 % lower as compared to intake with food. Therefore, darunavir tablets should be taken with ritonavir and with food. The type of food does not affect exposure to darunavir.

Distribution:

Darunavir is approximately 95 % bound to plasma protein. Darunavir binds primarily to plasma alpha-1-acid glycoprotein.

Metabolism**:**

In-vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by isozyme CYP3A4. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir/rtv dose was due to the parent substance. At least three oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 10-fold less than the activity of darunavir against wild type HIV.

Elimination:

After a 400/100 mg ^{14}C-darunavir/rtv dose, approximately 79,5 % and 13,9 % of the administered dose of ^{14}C-darunavir could be retrieved in faeces and urine, respectively. Unchanged darunavir accounted for approximately 41,2 % and 7,7 % of the administered dose in faeces and urine respectively. The terminal elimination half-

life of darunavir was approximately 15 hours when combined with ritonavir. The intravenous clearance of darunavir alone (150 mg) and in the presence of low-dose ritonavir was 32,8 L/h and 5,9 L/h, respectively.

Special patient populations:

Paediatrics

The pharmacokinetics of darunavir in combination with ritonavir in 74 treatment-experienced paediatric patients, aged six to < 18 years and weighing at least 20 kg, showed that the administered weight-based dosages resulted to darunavir exposure comparable to that in adults receiving darunavir/rtv 600/100 mg twice daily.

Elderly

Population pharmacokinetics analysis in HIV-infected patients showed that darunavir pharmacokinetic are not much different in the age range (18 to 75 years) evaluated in HIV infected patients (n = 12, age ≥ 65) (see **section 4.4**)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[PARANVIR] 75/ 150 film-coated tablets

Tablet core

Silicified microcrystalline cellulose

Crospovidone

Colloidal silicon dioxide

Magnesium stearate

Tablet film-coat

Opadry white

[PARANVIR] 400/ 600 film-coated tablets

Tablet core

Silicified microcrystalline cellulose

Crospovidone

Colloidal silicon dioxide

Magnesium stearate

Tablet film-coat

Opadry II orange

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30°C

KEEP OUT OF THE REACH OF CHILDREN

6.5 Nature and contents of container

PARANVIR 75: 150 cc HDPE bottle with a 38 mm non child-resistant closure containing 480 Tablets per carton

PARANVIR 150: 150 cc HDPE bottle with a 38 mm non child-resistant closure containing 240 tablets per carton

PARANVIR 400: 85 cc HDPE bottle with a 38 mm non child-resistant closure containing 60 tablets per carton

PARANVIR 600: 150 cc HDPE bottle with a 38 mm non child-resistant closure containing 60 tablets per carton

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage or disposal conditions.

7. MARKETING AUTHORISATION HOLDER

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

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8. MARKETING AUTHORISATION NUMBER(S)

PARANVIR 75: 50/20.2.8/0609

PARANVIR 150: 50/20.2.8/0610

PARANVIR 400: 50/20.2.8/0611

PARANVIR 600: 50/20.2.8/0612

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 April 2020

10. DATE OF REVISION OF THE TEXT

TBC