APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NURADAR 600 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NURADAR 600 mg:

Each film-coated tablet contains darunavir propylene glycolate equivalent to darunavir 600 mg.

Sugar free.

3. PHARMACEUTICAL FORM

NURADAR 600 mg:

Orange coloured, oval shaped, biconvex, film-coated tablets debossed with 'D' on one side and '600' on another side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NURADAR, in combination with 100 mg ritonavir (NURADAR /rtv) 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 darunavir and ritonavir indicated a greater reduction of plasma HIV RNA levels and greater increase in CD4+ cell counts when compared to a protease inhibitor (PI) regimen of choice, each given in combination with other antiretrovirals.

There is no information on the use of darunavir /rtv (600/100) in HIV-infected paediatric patients and in antiretroviral treatment-naïve adult patients. Treatment history and, when available, genotypic or phenotypic testing should guide the use of NURADAR /rtv.

4.2. Posology and method of administration

Treatment with NURADAR should be initiated by a medical practitioner experienced in the management of HIV infection.

Posology

NURADAR must always be given with 100 mg ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicines. The prescribing information of ritonavir including the contraindications and warnings must therefore be consulted prior to initiation of therapy with NURADAR /rtv

Adults:

The recommended dosage of NURADAR is one 600 mg tablet twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect the exposure to darunavir. Ritonavir (100 mg twice daily) is used as a pharmacokinetic enhancer of darunavir (see section 4.5 and section 5.2). A further increase in the dose of NURADAR or ritonavir has been shown not to result in any clinically relevant increase in antiviral activity.

NURADAR must always be used with 100 mg of ritonavir in combination with other antiretroviral medicines. Patients should not alter the dose of either NURADAR or ritonavir, discontinue ritonavir, or discontinue therapy with NURADAR without consulting their medical practitioner. If a patient misses a dose of NURADAR or ritonavir by more than 6 hours, the patient should be told to wait and then take the next dose of NURADAR and ritonavir at the regularly scheduled time. If the patient misses a dose of NURADAR or ritonavir by less than 6 hours, the patient should be told to take NURADAR and ritonavir immediately, and then take the next dose of NURADAR and ritonavir at the regularly scheduled time. If a dose of NURADAR or ritonavir is skipped, the

patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of NURADAR or ritonavir at any one time.

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

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

Hepatic impairment:

No dose adjustment is required in patients with mild or moderate hepatic impairment. There is no data regarding the use of darunavir/rtv when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made.

NURADAR /rtv 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).

Method of administration

NURADAR should be administered orally with ritonavir and food. Failure to correctly administer NURADAR with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect. The type of food does not affect exposure to NURADAR. Patients should be instructed to swallow whole tablets with a drink such as water or milk.

4.3. Contraindications

- Hypersensitivity to darunavir or to any of the excipients of NURADAR listed in section 6.1.
- The presence of a contraindication to ritonavir.
- Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A (CYP3A) isoforms. NURADAR/ rtv should not be co-administered with medicines that are highly dependent on CYP3A for clearance and for which increased plasma

concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

These medicines are included in the table below:

Medicines that are contraindicated with NURADAR/ /rtv	
Medicine Class: Medicine Name	Clinical Comment
Anticonvulsants: Carbamazepine, Phenobarbitone, Phenytoin	Carbamazepine, phenobarbitone and phenytoin are inducers of CYP450 enzymes. NURADAR/ /rtv should not be used in combination with Phenobarbitone, phenytoin or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of NURADAR (see section 4.5).
Antihistamines: Astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Antimycobacterial: Rifampicin Rifabutin	Rifampicin is a potent inducer of CYP450 metabolism. NURADAR/rtv should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of NURADAR (see section 4.5). The exposure to rifabutin and its active metabolite was increased 3-fold and the incidence of side effects was doubled when rifabutin was given at a

	dose of 150 mg every other day in combination with NURADAR and ritonavir (see section 4.5).
Endothelin receptor antagonist: Bosentan	Concomitant use of bosentan and NURADAR /rtv should be avoided (see section 4.5).
PDE5 inhibitors: Sildenafil - for treatment of pulmonary arterial hypertension	A safe and effective dose of sildenafil for the 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).
Avanafil	CONTRAINDICATED
Antigout: Colchicine in patients with hepatic or renal impairment	Co-administration of NURADAR /rtv in patients with renal or hepatic impairment is contraindicated due to the potential risk of colchicine-induced toxic effects.
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension
Ergot Derivatives: Dihydroergotamine, Ergonovine, Ergotamine,	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral

Methylergonovine	vasospasm and ischaemia of the extremities and other tissues.
GI Motility Medicines: Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Hepatitis C virus (HCV) direct-acting antivirals: NS3-4A protease inhibitors Boceprevir Telaprevir Elbasvir/ grazoprevir	It is not recommended to co-administer NURADAR/rtv with boceprevir or telaprevir (see section 4.5).
Herbal Products: St. John's Wort (Hypericum perforatum)	NURADAR/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. This may result in loss of the therapeutic effect of NURADAR (see section 4.5).
HMG-CoA Reductase Inhibitors: Lovastatin, Simvastatin	Potential for serious reactions such as risk of myopathy, including rhabdomyolysis
Neuroleptic: Pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.

Sedative-Hypnotics: Midazolam, Triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Antifungals: Ketoconazole, itraconazole and voriconazole	CONTRAINDICATED because concomitant systemic use of ketoconazole, itraconazole or voriconazole and NURADAR/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by NURADAR/rtv, while the plasma concentrations of voriconazole may be decreased in the presence of NURADAR/rtv (see section 4.5)
Buprenorphine/naloxone:	The results of an interaction trial with NURADAR/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with NURADAR/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if NURADAR/rtv and buprenorphine are co-administered (see section 4.5).
Other medicines - Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine	CONTRAINDICATED, co-administration results in increased concentrations' of the co-administered medicines.

- Dapoxetine - Domperidone - Naloxegol - Lurasidone, pimozide, quetiapine, sertindole - Dabigatran, ticagrelor	

4.4. Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Appropriate precautions should continue to be employed.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a medical practitioner while using NURADAR.

General

Please refer to ritonavir prescribing information for additional information on precautionary measures.

Skin rash

During the clinical development programme, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported. Stevens Johnson Syndrome has also been rarely reported and during post-marketing experience toxic epidermal necrolysis has been reported very rarely. Discontinue NURADAR 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**.** Rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in patients using darunavir/rtv was 0,5 %.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/rtv + raltegravir compared to subjects receiving darunavir /rtv without raltegravir or raltegravir without darunavir/rtv. However, rash that was considered medicine related occurred at similar rates for all three groups.

Sulpha allergy

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

Interactions

NURADAR and ritonavir are both inhibitors of CYP3A. Co administration of NURADAR/rtv with 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 (see section 4.3 and section 4.5).

Efavirenz in combination with boosted NURADAR once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with NURADAR, the NURADAR/ritonavir 600/100 mg twice daily regimen should be used (see section 4.5)

Diabetes mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving darunavir. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued NURADAR, hyperglycaemia persisted in some

cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between darunavir and these events have not been established. Consideration should be given to the monitoring of blood glucose.

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).

PDE5 inhibitors:

The phosphodiesterase type 5 (PDE5) inhibitors sildenafil, vardenafil and tadalafil are highly dependent on CYP3A for their metabolism. If concomitant use of NURADAR/rtv with sildenafil, vardenafil or tadalafil is indicated, reduced doses of the PDE5 inhibitors are recommended (see section 4.5).

Elderly:

As limited information is available on the use of NURADAR/rtv in patients aged 65 and over, caution should be exercised in the administration of NURADAR in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg NURADAR was given orally in combination with ritonavir at 100 mg twice daily. Therefore, NURADAR should only be used in combination with 100 mg of ritonavir as a pharmacokinetic enhancer (see section 5.2). Increasing the dose of ritonavir did not significantly affect darunavir concentrations and is not recommended.

Patients with coexisting conditions

Hepatic impairment

There is no data regarding the use of NURADAR/rtv when co-administered to patients with

severe hepatic impairment; therefore, NURADAR should not be used. No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 4.2 and section 5.2).

Hepatotoxicity

Medicine-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with NURADAR/rtv. Patients with pre-existing liver dysfunction, 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 NURADAR/rtv and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis or cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of NURADAR/rtv 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, hepatomegaly) in patients on NURADAR/rtv should prompt consideration of interruption or discontinuation of 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 and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.2 and section 5.2).

Haemophiliac patients

There have been reports of increased bleeding, including spontaneous skin haematomas and haem arthrosis in patients with haemophilia type A and B treated with PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with PIs was

continued or reintroduced if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Fat redistribution and metabolic disorders

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum 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.

Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. 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 (see section 4.8)

Immune reactivation syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses 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 first 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, atypical mycobacterial infections, cytomegalovirus retinitis, *Pneumocytis jirovecii (carini)* pneumonia and cryptococcal meningitis.

Appropriate treatment of the 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 Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

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

Opportunistic infections

Patients receiving NURADAR 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 NURADAR, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Resistance/Cross-resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully

explored in darunavir/rtv-treated patients, it is unknown what effect therapy with NURADAR will have on the activity of subsequently administered protease inhibitors.

4.5. Interaction with other medicines and other forms of interaction

Darunavir and ritonavir inhibits, and is extensively metabolised by the cytochrome P450 isoenzyme and CYP3A4. It may affect the clearance of other medicines metabolised by this enzyme, potentially resulting in increased plasma concentrations and toxicity.

NURADAR/rtv should not be co-administered with medicines that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicines include 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. NURADAR/rtv should not be used in combination with rifampicin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of the therapeutic effect of NURADAR (see section 4.3).

Herbal products

NURADAR/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. This may result in loss of the therapeutic effect of NURADAR (see section 4.3).

Antiretroviral medicines

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

Didanosine

Darunavir/rtv (600/100 mg twice daily) did not significantly affect didanosine exposure. The combination of NURADAR co-administered with 100 mg 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 1 hour before or 2 hours after NURADAR/rtv (which are administered with food).

Tenofovir

The results of an interaction trial 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/rtv (300/100 mg twice daily). This finding is not considered to be clinically relevant. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustments of NURADAR, ritonavir 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, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no medicine interactions are expected for these medicines and NURADAR/rtv.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine

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

Efavirenz

An interaction trial between darunavir/rtv (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 NURADAR/rtv. The combination of darunavir/rtv and efavirenz should be used with caution (see section 4.4)

Nevirapine

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

Rilpivirine

In an interaction trial between NURADAR/rtv (800/100 mg once daily) and rilpivirine (150 mg once daily), no clinically relevant effect on darunavir exposure was observed. Exposure to rilpivirine increased by 130 % (2,3-fold) when administered in combination with NURADAR/rtv. Since this difference is not considered to be clinically relevant, the combination of darunavir/rtv and rilpivirine can be used without dose adjustments.

Protease inhibitors (PIs)

Ritonavir

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, NURADAR 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 trials with darunavir with or without ritonavir and lopinavir/ritonavir (1 200 mg darunavir twice daily with or without 100 mg ritonavir twice daily and lopinavir/ritonavir 400/100 mg twice daily or 533/133,3 mg twice daily) demonstrated a decrease in the exposure

(AUC) of darunavir by 40 %. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer NURADAR/rtv 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/rtv; saquinavir exposure was not affected by the presence of darunavir /rtv. It is not recommended to combine saquinavir and NURADAR (with or without low-dose ritonavir).

Atazanavir

An interaction trial between darunavir /rtv (400/100 mg twice daily) and atazanavir (300 mg once daily) and ritonavir 100 mg once daily demonstrated that systemic exposure to darunavir and atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with NURADAR/rtv.

Indinavir

In an interaction study between darunavir /rtv (400/100 mg twice daily) and indinavir (800 mg twice daily), darunavir exposure was increased by 24 % in the presence of indinavir/rtv; indinavir exposure was increased by 23 % in the presence of darunavir /rtv. The appropriate dose of indinavir in combination with darunavir /rtv has not been established.

Other HIV protease inhibitors

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

CCR5 antagonist

When used in combination with NURADAR/rtv, the dose of maraviroc should be 150 mg twice daily. An interaction trial between NURADAR/rtv (600/100 mg twice daily) and maraviroc (150 mg twice daily) demonstrated that in the presence of NURADAR/rtv the exposure of maraviroc

was increased 4-fold. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.

Other medicines

Alfuzosin

Exposure to alfuzosin may be increased when co-administered with NURADAR/rtv. Concomitant use of NURADAR/rtv with alfuzosin is contraindicated (see section 4.3)

Antidysrhythmics (bepridil, systemic lidocaine, quinidine and amiodarone)

Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with NURADAR/rtv. This can lead to prolongation or an increase of their therapeutic effect and adverse events (see section 4.3). Caution is warranted and therapeutic medicine monitoring of antidysrhythmics, if available, is recommended, when co-administered with NURADAR/rtv.

Digoxin

An interaction trial with darunavir /rtv (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 NURADAR/rtv. Serum digoxin concentrations should be monitored to assist in the titration.

Anticoagulants

Warfarin

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

Apixaban, Edoxaban, Rivaroxaban

Co-administration of boosted NURADAR with these anticoagulants may increase concentrations of the anticoagulant, which may lead to an increased bleeding risk. (CYP3A and/or P-gp inhibition). The use of boosted NURADAR and these anticoagulants is not recommended.

Dabigatran, Ticagrelor

Co-administration with boosted NURADAR may lead to a substantial increase in exposure to dabigatran or ticagrelor. Concomitant administration of boosted NURADAR with dabigatran or ticagrelor is contraindicated (see section 4.3). Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended.

Anticonvulsants (phenobarbitone, phenytoin and carbamazepine)

Phenobarbitone, phenytoin and carbamazepine are inducers of CYP450 enzymes. NURADAR/rtv 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 the therapeutic effect of NURADAR (see section 4.3).

Colchicine

Concomitant use of colchicine and NURADAR/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout flares in patients on NURADAR/rtv, the recommended dose of colchicine is 0,6 mg (1 tablet), followed by 0,3 mg (half tablet) 1 hour later. The treatment course is to be repeated no earlier than 3 days. For the prophylaxis of gout flares in patients on NURADAR/rtv, the recommended dose of colchicine is 0,3 mg every day or every other day. For the treatment of familial Mediterranean fever in patients on NURADAR/rtv, the maximum dose of colchicine is 0,6 mg every day (may be given as 0,3 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with NURADAR/rtv.

Calcium channel blockers

The exposure to calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase

when NURADAR/rtv are used concomitantly. Caution is warranted and careful clinical monitoring is recommended.

Clarithromycin

An interaction trial between darunavir/rtv (400/100 mg twice daily) and clarithromycin (500 mg twice daily) showed a 57 % increase in exposure to clarithromycin, 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 adjustments should be considered:

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

Dexamethasone

Systemic 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 (endothelin receptor antagonist)

Concomitant use of bosentan and NURADAR/rtv may increase plasma concentrations of bosentan. In patients who have been receiving NURADAR/rtv for at least 10 days, bosentan should be started at 62, 5 mg once daily or once daily on every alternate day, based upon individual tolerability. For patients on bosentan and initiating NURADAR/rtv, the use of bosentan should be discontinued at least 36 hours prior to initiation of NURADAR/rtv. After at least 10 days following the initiation of NURADAR/rtv, bosentan should be resumed at 62,5 mg once daily or once daily on every alternate day based upon individual tolerability

Fluticasone

Concomitant use of boosted NURADAR and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Co-administration with CYP3A metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects.

Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are expected to have markedly increased plasma concentrations when co-administered with NURADAR/rtv. Increased concentrations of HMG CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of NURADAR/rtv with lovastatin and simvastatin is therefore not recommended.

The results of an interaction trial with atorvastatin show that atorvastatin (10 mg once daily) in combination with darunavir /rtv (300/100 mg twice daily) provides an exposure to atorvastatin that is only 15 % lower than that obtained with atorvastatin (40 mg once daily) alone. When administration of atorvastatin and NURADAR/rtv 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 /rtv (600/100 mg twice daily) increased exposure to a single dose of pravastatin (40 mg) by approximately 80 %. However, in a subset of subjects the pravastatin exposure was increased 5-fold. Until more information is available regarding this

interaction and the underlying mechanism, it is not recommended that pravastatin be co-administered with NURADAR/rtv.

H_2-Receptor antagonists and proton pump inhibitors

Co-administration of omeprazole (20 mg once daily) or ranitidine (150 mg twice daily) and darunavir /rtv (400/100 mg twice daily) did not affect the exposure to darunavir. Based on these results, NURADAR/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without dose adjustments.

Inhaled beta agonist

Salmeterol

Concomitant use of salmeterol and NURADAR/rtv is not recommended. The combination may result in an increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Immunosuppressants (ciclosporin, tacrolimus, sirolimus)

Exposure to ciclosporin, tacrolimus, or sirolimus may be increased when co-administered with NURADAR/rtv. Therapeutic medicine monitoring of the immunosuppressant is recommended when co-administered with NURADAR/rtv.

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 NURADAR/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by NURADAR/rtv. The concomitant administration of ketoconazole (200 mg twice daily) with darunavir /rtv (400/100 mg twice daily) increased exposure of ketoconazole and darunavir by 212 % and 42 %, respectively. Concomitant use of ketoconazole, itraconazole and voriconazole with NURADAR 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 NURADAR/rtv (see section 4.3).

Methadone

An interaction trial investigating the effect of darunavir /rtv (600/100 mg twice daily) on a stable methadone maintenance therapy showed an AUC decrease of 16 % for R-methadone.

Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of NURADAR/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients (see section 4.3)

Buprenorphine/naloxone

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

Oestrogen-based contraceptives

The results of an interaction trial between darunavir /rtv (600/100 mg twice daily) and ethinylestradiol (35 mcg) and norethindrone (1 mg) demonstrated that at steady-state 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 4.3)

PDE5 inhibitors

Treatment of erectile dysfunction

In an interaction trial 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 /rtv (400/100 mg twice daily). Concomitant use of PDE5 inhibitors for the treatment of erectile dysfunction with NURADAR/rtv should be done with caution. If concomitant use of NURADAR/rtv with sildenafil, vardenafil, or tadalafil is indicated, reduced doses of the PDE5 inhibitors are recommended.

If concomitant use of NURADAR/rtv with sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a 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 4.3).

The combination of avanafil and boosted NURADAR is contraindicated (see section 4.3).

Treatment of pulmonary arterial hypertension

A safe and effective dose of sildenafil for the 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 NURADAR/rtv with sildenafil when used for pulmonary arterial hypertension is contraindicated (see section 4.3).

For the treatment of pulmonary arterial hypertension with tadalafil co-administered with NURADAR/rtv, a dose adjustment for tadalafil is warranted. In patients who have been receiving NURADAR/rtv for at least 1 week, start tadalafil at 20 mg every day, and increase to 40 mg every day based upon individual tolerability. For patients on tadalafil and initiating NURADAR/rtv, discontinue the use of tadalafil at least 24 hours prior to initiating NURADAR/rtv and avoid the use of tadalafil during the initiation of NURADAR/rtv. After at least 1 week following the initiation of NURADAR/rtv, resume tadalafil at 20 mg every day and increase to 40 mg every day based upon individual tolerability.

Rifabutin

Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and NURADAR/rtv is expected to increase rifabutin exposure and decrease darunavir exposure. When indicated, it is recommended that rifabutin be administered at a dosage of 150 mg once every other day when combined with NURADAR/rtv.

Selective Serotonin Reuptake Inhibitors (SSRIs)

In an interaction trial between paroxetine (20 mg once daily) or sertraline (50 mg once daily) and darunavir /rtv (400/100 mg twice daily), 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 /rtv. If SSRIs are co-administered with

NURADAR/rtv, the recommended approach 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 NURADAR/rtv should be monitored for antidepressant response.

Antidepressants (Trazodone)

Concomitant use of trazodone and NURADAR/rtv 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 NURADAR/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.

Antimalarials

Artemether/Lumefantrine

The combination of boosted NURADAR and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in lumefantrine exposure, the combination should be used with caution.

Hepatitis C Virus (HCV) Direct-acting antivirals

NS3-4A protease inhibitors

Elbasvir/ grazoprevir

Concomitant use of boosted NURADAR and elbasvir/grazoprevir is contraindicated (see section 4.3).

Boceprevir

In an interaction trial between darunavir/ rtv (600/100 mg twice daily) and boceprevir (800 mg three times daily), darunavir exposure was reduced by 44 % and boceprevir exposure was reduced by 32 %. It is not recommended to co-administer boosted NURADAR and boceprevir (see section 4.3)

Glecaprevir/pibrentasvir

It is not recommended to co-administer boosted NURADAR with glecaprevir/ pibrentasvir.

Simeprevir

It is not recommended to co-administer boosted NURADAR and simeprevir.

Telaprevir

In an interaction trial between darunavir/rtv (600/100 mg twice daily) and telaprevir (750 mg every 8 hours), darunavir exposure was reduced by 40 % and telaprevir exposure was reduced by 35 %. It is not recommended to co-administer NURADAR/rtv with telaprevir (see section 4.3).

Treatment for premature ejaculation

Dapoxetine

Co-administration of boosted NURADAR with dapoxetine is contraindicated (see section 4.3).

Antihistamines

Astemizole

Exposure to these antihistamines may be increased when co-administered with [PRODUCT NAM] /rtv. Concomitant use of darunavir /rtv with astemizole is contraindicated (see CONTRAINDICATIONS)

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy have 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 if they are receiving NURADAR.

Fertility

There was no effect on mating or fertility with NURADAR treatment in rats.

4.7. Effects on ability to drive and use machines

Dizziness has been reported in some patients during treatment with regimens containing NURADAR/rtv and this should be borne in mind when considering a patient's ability to drive or operate machinery when treated with NURADAR/ rtv.

4.8. Undesirable effects

Infections and infestations:

Less frequent: Herpes simplex

Blood and lymphatic system disorders:

Less frequent: thrombocytopenia, neutropenia, anaemia, leukopenia,

Rare: increased eosinophil count

Immune system disorders:

Less frequent: Immune reconstitution inflammatory syndrome, (drug) hypersensitivity

Endocrine disorders:

Less frequent: hypothyroidism, increased blood thyroid stimulating hormone

Metabolism and nutrition disorders:

Frequent: Diabetes mellitus, anorexia, hypertriglyceridemia, hypercholesterolemia, hyperlipidaemia, hyperglycaemia

Less frequent: Gout, decreased appetite, decreased weight, increased weight, hyperglycaemia, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase

Psychiatric disorders:

Frequent: insomnia

Less frequent: Abnormal dreams, depression, disorientation, anxiety, sleep disorder, nightmare, decreased libido,

Rare: confusional state, altered mood, restlessness

Nervous system disorders:

Frequent: Headache, peripheral neuropathy, dizziness

Less frequent: lethargy, paraesthesia, hypoaesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence

Rare: syncope, convulsion, ageusia, sleep phase rhythm disturbance

Eye disorders:

Less frequent: conjunctival hyperaemia, dry eye,

Rare: visual disturbance

Ear and labyrinth disorders:

Less frequent: vertigo

Cardiac disorders:

Less frequent: Myocardial infarction, angina pectoris, prolonged electrocardiogram QT, tachycardia, *Rare:* acute myocardial infarction, sinus bradycardia, palpitations

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea, cough, epistaxis, throat irritation

Rare: rhinorrhoea

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, abdominal pain, vomiting, dyspepsia, abdominal distension, flatulence

Less frequent: Acute pancreatitis, gastritis, gastroesophageal reflux disease, aphthous stomatitis, retching, dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysesthesia

Rare: stomatitis, hematemesis, cheilitis, dry lip, coated tongue

Hepatobiliary disorder:

Frequent: increased alanine aminotransferase

Less frequent: Acute hepatitis, hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gammaglutamyltransferase

Skin and subcutaneous tissue disorders:

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

Less frequent: angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation

Rare: DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma

Frequency unknown: toxic epidermal necrolysis, acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders:

Frequent: Myalgia

Less frequent: Osteonecrosis, muscle spasms, muscular weakness, arthralgia, pain in extremity, osteoporosis, and increased blood creatine phosphokinase

Rare: musculoskeletal stiffness, arthritis, joint stiffness

Renal and urinary disorders:

Less frequent: acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria

Rare: decreased creatinine 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 oedema, malaise, feeling hot, irritability, pain

Rare: chills, abnormal feeling, xerosis

Additional adverse reactions in other clinical trials

System Organ Class & Frequency Category	**Adverse Reaction**
Skin and subcutaneous tissue disorders	
uncommon:	Stevens-Johnson Syndrome

POST-MARKETING EXPERIENCE

Adverse drug reactions identified during post-marketing experience.

System Organ Class	**Adverse Drug Reaction**
Immune system disorders	Hypersensitivity
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis Angioedema, urticaria
Musculoskeletal and connective tissue disorders	Osteonecrosis

a. Description of selected adverse events

Rash

In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. During the clinical development program of raltegravir in treatment-experienced

patients, rash, irrespective of causality, was more commonly observed with regimens containing NURADAR/rtv + raltegravir compared to those containing NURADAR/rtv without raltegravir or raltegravir without NURADAR/rtv.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Musculoskeletal abnormalities

Increased CPK, myalgia, myositis and rarely, rhabdomyolysis have been reported with the use of protease inhibitors, particularly in combination with NRTIs.

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

Immune reconstitution inflammatory syndrome

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

Bleeding in haemophiliac patients

There have been reports of increased spontaneous bleeding in haemophiliac patients receiving antiretroviral protease inhibitors (see section 4.4).

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

patients co-infected with hepatitis B or C were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis (see section 4.4)

a. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the

"**6.04 Adverse Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms

Human experience of acute overdose with NURADAR/rtv is limited.

Treatment

There is no specific antidote for overdose with NURADAR. Treatment of overdose with NURADAR consists 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. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 20.2.8 Antiviral agents

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 tightly binds 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, human 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). Darunavir demonstrated antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC50 values ranging from < 0,1 to 4,3 nM. These EC50 values are well below the 50 % cellular toxicity concentration range of 87 µM to > 100 µM.

The EC_{50} value of darunavir increases by a median factor of 5,4 in the presence of human serum. Darunavir showed synergistic antiviral activity when studied in combination with the protease inhibitors ritonavir, nelfinavir or amprenavir and additive antiviral activity when studied in combination with the protease inhibitors indinavir, saquinavir, lopinavir, atazanavir or tipranavir, the N(t)RTIs zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, emtricitabine or tenofovir, the NNRTIs nevirapine, delavirdine or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of these antiretrovirals.

Resistance in vitro

In vitro darunavir-resistant virus isolates from wild type HIV-1 were selected. Viruses showing decreased susceptibility to darunavir (range: 6 to 21-fold) harboured 3 to 6 amino acid

substitutions in the 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 to 641-fold change in EC50 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, I47V, I50V, L63P, A71V and I84V were present in more than 50 % of the nine darunavir-resistant isolates. A minimum of eight of these darunavir in vitro selected mutations, from which at least two were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (multifold change [FC] > 10) to darunavir.

In 1 113 clinical isolates resistant to at least one protease inhibitor and in 886 baseline isolates from the patients enrolled in the clinical trials only the subgroups with > 10 PI resistance associated mutations showed a median FC for darunavir > 10.

Cross-resistance in vitro

Cross-resistance has been observed among protease inhibitors. Darunavir has a < 10-fold decreased susceptibility to 90 % of 3 309 clinical isolates resistant to at least one protease inhibitor.

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors or the fusion inhibitor 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 to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir is rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low-dose ritonavir is generally achieved within 2,5 to 4,0 hours.

The absolute oral bioavailability of a 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 an approximate 14-fold increase in the systemic exposure of darunavir when a 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 active 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 human immunodeficiency virus (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 Populations

Paediatrics

There is no information on the pharmacokinetics of darunavir in combination with ritonavir in paediatric subjects.

Elderly

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

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure (16,8 %) in HIV infected females compared to males. This difference is not clinically relevant.

Renal impairment

Results from a mass balance study with 14C-darunavir/rtv showed that approximately 7,7 % of the administered dose of darunavir is excreted in the urine as unchanged active substance.

Darunavir has not been studied in patients with renal impairment.

Hepatic impairment

Darunavir is primarily metabolised and eliminated by the liver. In a multiple-dose study with darunavir co-administered with ritonavir (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild (Child-Pugh Class A, n=8) hepatic impairment were comparable with those in healthy subjects. In moderate hepatic impairment (Child-Pugh Class B, n=8) the mean C_{max} was increased by 22 %, the AUC by 20 % and the C_{min} by 27 % after multiple doses. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see section 4.2 and section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The other ingredients of NURADAR are cellulose microcrystalline, crospovidone, hydroxypropyl cellulose, magnesium stearate and silica colloidal anhydrous.

In addition NURADAR 600 mg contains Opadry® II complete film coating system 85F13962 orange.

Nuradar 600 mg:

Opadry® II complete film coating system 85F13962 orange contains FD&C Yellow #6 (C.I. No. 15985), macrogol, talc and titanium dioxide (C.I. No. 77891).

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store at or below 25 °C

Keep HDPE containers tightly closed

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

NURADAR 600 mg:

Tablets are packed in white opaque round 100 ml HDPE container with 38 mm neck finish closed with white opaque polypropylene 38 mm - SP 400 child resistant closure with wad having TEKNIPLEX HS 123 induction sealing liner.

Pack size: 30's - One HDPE container contains 30 tablets.

6.6. Special precautions for disposal and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Aurobindo Pharma (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

53/20.2.8/0240

9. DATE OF FIRST AUTHORISATION

18 August 2020