CLEAN PROFESSIONAL INFORMATION FOR VUNAD 400/800

SCHEDULING STATUS [S4]

1 NAME OF THE MEDICINE

VUNAD 400 & 800 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 & 800 mg of Darunavir.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Darunavir 400 mg Tablets:

Yellow, oval shaped, biconvex, film- coated tablets de-bossed with 'V' on one side and '4' on the other side.

Size of tablet: 15,78 mm (L) X 7,94 mm (W).

Darunavir 800 mg Tablets:

Yellow, oval shaped, biconvex, film- coated tablets de-bossed with 'V' on one side and '7' on the other side.

Size of tablet: 20,24 mm (L) X 10,20 mm (W).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VUNAD, in combination with low dose ritonavir (VUNAD/rtv) 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-naïve patients or after exclusion of darunavir

resistance associated mutations (DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).

Genotypic or phenotypic testing should guide the use of **VUNAD**/rtv.

Ritonavir is used as a pharmacokinetic enhancer of darunavir.

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

4.2 Posology and method of administration

Posology:

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

Adults:

Genotypic or phenotypic testing should guide the use of

VUNAD/rtv. **VUNAD**/ ritonavir 800/100 mg once

Daily dosing regimen is recommended in HIV mg once daily dosing regimen is recommended in HIV protease-inhibitor-naïve patients and in treatment- experienced patients with demonstrated absence of DRV- RAMs. **VUNAD** should be given with food. The type of food does not affect the exposure to darunavir.

Ritonavir (100 mg) is used as a pharmacokinetic enhancer of darunavir (see section 4.5 and 5.2).

Missed Dose(s):

In case a dose of **VUNAD** and/or ritonavir was missed within 12 hours of

the time it is usually taken, patients should be instructed to take the prescribed dose of **VUNAD** and ritonavir with food as soon as possible. If this was noticed later than 12 hours after the time it is usually

taken, the missed dose should not be taken, and the patient should resume the usual dosing schedule.

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 **VUNAD**/rtv when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. **VUNAD**/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 5.2).

Paediatric population:

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 **VUNAD**/rtv in paediatric patients has not been established.

Method of administration:

PN is to be administered orally.

4.3 Contraindications

Hypersensitivity to darunavir or to any of the excipients listed in section 6.1.

The presence of a contraindication to ritonavir.

Patients with severe (Child-Pugh Class C) hepatic impairment.

Concomitant treatment with any of the following medicinal products given the expected decrease in plasma concentrations of **VUNAD**, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and4.5).

Applicable to **VUNAD** boosted with either ritonavir or cobicistat:

- The combination product lopinavir/ritonavir (see section 4.5).

- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (Hypericum perforatum). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

VUNAD boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to **VUNAD** boosted with either ritonavir or cobicistat). These active substances include e.g.:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine
- colchicine when used in patients with renal and/or hepatic impairment (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- elbasvir/grazoprevir
- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)
- triazolam, midazolam administered orally (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil
- simvastatin, lovastatin and lomitapide (see section 4.5)
- dabigatran, ticagrelor (see section 4.5).

4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy, including VUNAD, does not prevent the

risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Elderly

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

General

VUNAD must be co-administered with ritonavir and food to exert its therapeutic effect (see Section 4.2). Failure to correctly administer **VUNAD** with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

VUNAD should 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.

Severe skin reactions

During the clinical development program, severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported. Stevens-Johnson Syndrome has been reported; and during post-marketing experience toxic epidermal necrolysis has also been reported. **VUNAD** should be discontinued 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 **VUNAD**. The discontinuation rate due to rash in patients using **VUNAD**/rtv was 0,5 %. Rash occurred more commonly in treatment-experienced subjects receiving regimens containing **VUNAD**/rtv

+ raltegravir compared to subjects receiving **VUNAD**/rtv without raltegravir or raltegravir without **VUNAD**/rtv. However, rash that was considered medicine related occurred at similar rates for all three groups.

Sulpha allergy

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

Patients with coexisting conditions

Hepatic impairment

VUNAD should not be used in patients with severe hepatic impairment. 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 **VUNAD**/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 **VUNAD**/rtv 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 elevations of transaminases, especially during the first several months of **VUNAD**/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, liver tenderness, hepatomegaly) in patients on **VUNAD**/rtv should prompt consideration of interruption or discontinuation of treatment.

Renal impairment

Since the renal clearance of darunavir is limited, a decrease in the elimination of **VUNAD** 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).

Haemophilia patients:

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

Hyperglycaemia

New onset diabetes mellitus, hyperglycaemia, or exacerbation of pre-existing diabetes mellitus has been reported in patients receiving **VUNAD**.

Lipodystrophy and metabolic abnormalities

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.

Immune Reconstitution Inflammatory 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, cytomegalovirus retinitis, 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 **VUNAD** 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.

Interactions with medicines

VUNAD and ritonavir are both inhibitors of CYP3A. Co-administration of **VUNAD**/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).

For medicines that are highly dependent on the 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 **VUNAD**/rtv. This can lead to prolongation or increase of their therapeutic effect and adverse events (see section 4.5).

HMG-CoA Reductase Inhibitors

Concomitant use of **VUNAD**/rtv with simvastatin, pravastatin or lovastatin is not recommended due to an

increased risk of myopathy, including rhabdomyolysis, as a consequence of increased plasma concentrations of simvastatin, pravastatin or lovastatin.

Methadone

No adjustment of methadone dosage is required when initiating co-administration of **VUNAD**/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted (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

If concomitant use of **VUNAD**/rtv with sildenafil, vardenafil, or tadalafil is indicated, reduced doses of the PDE-5 inhibitors are recommended (see section 4.3 and section 4.5).

Paediatric population:

VUNAD is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight (see sections 4.2 and 5.3).

4.5 Interaction with other medicines and other forms of interaction

Darunavir and ritonavir are both inhibitors of the cytochrome CYP3A. Co-administration of **VUNAD** and ritonavir 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.

VUNAD/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 astemizole, 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. **VUNAD**/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 therapeutic effect to **VUNAD** (see Section 4.3 and 4.4).

VUNAD/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 therapeutic effect to PREZISTA (see Section 4.3 and 4.4).

Antiretroviral medicinal products

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

Didanosine

VUNAD/rtv 100 mg twice daily) did not significantly affect didanosine exposure. The combination of **VUNAD** 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 1 hour before or 2 hours after **VUNAD**/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. There was no change in the urinary excretion of tenofovir or darunavir during co-administration. Tenofovir did not have a clinically significant influence on darunavir exposure.

No dose adjustments of **VUNAD**, ritonavir, or tenofovir disoproxil fumarate are required when these medicines are co-administered.

Other NRTIs

Based on the different elimination pathways of other NRTIs such as zidovudine, zalcitabine,

emtricitabine, stavudine, lamivudine and abacavir that are primarily renally excreted, no medicine interactions are expected for these medicinal compounds and **VUNAD**/rtv.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine

In an interaction trial between darunavir**/**rtv (100 mg twice daily) and etravirine, there was a 37 % decrease in etravirine exposure in the presence of **darunavir**/rtv and no relevant change in exposure to darunavir. Therefore, VUNAD/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 Cmin by 31 %

were observed. Exposure to efavirenz was increased by 21 % when administered in combination with darunavir/rtv. The combination of **VUNAD**/rtv and efavirenz should be used with caution.

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 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 darunavir/rtv and nevirapine can be used without dose adjustments.

Rilpivirine

In an interaction trial between darunavir/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 darunavir/rtv.

Since this difference is not considered to be clinically relevant, the combination of **VUNAD**/rtv and

rilpivirine can be used without dose adjustments.

HIV 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 darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, **VUNAD** should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer (see section 4.4 and 5.2).

Lopinavir/ritonavir

Results of interaction trials with darunavir **with** or without ritonavir

and lopinavir/ritonavir (1200 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 **VUNAD**/rtv with lopinavir/ritonavir.

Saquinavir

In an interaction trial 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 **VUNAD**, with or without low dose ritonavir.

Atazanavir

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

Indinavir

In an interaction trial 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.

Other HIV protease inhibitors

The co-administration of **VUNAD**/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 **VUNAD**/rtv, the dose of maraviroc should be 150 mg twice daily.

An interaction trial between darunavir/rtv (100 mg twice daily) and maraviroc (150 mg twice daily) demonstrated that in the presence of darunavir/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 **VUNAD**/rtv. Concomitant use of **VUNAD**/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 coadministered with **VUNAD**/rtv. Caution is warranted and therapeutic medicine monitoring of antidysrhythmics is recommended when **VUNAD** is administered with antidysrhythmic medicines.

Digoxin

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

Anticoagulants

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

Anticonvulsants (phenobarbitone, phenytoin and carbamazepine)

Phenobarbitone and phenytoin

Phenobarbitone and phenytoin are inducers of CYP450 enzymes. **VUNAD**/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 therapeutic effect to **VUNAD** (see section 4.3).

Carbamazepine

An interaction trial between darunavir/rtv (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 %. For carbamazepine, AUC_{12h} was increased by 45 %. No dose adjustment for **VUNAD**/rtv is recommended. If there is a need to combine **VUNAD**/rtv and carbamazepine, patients should be monitored for potential carbamazepine related adverse events. Carbamazepine concentrations should be monitored, and its dose should be titrated for adequate response.

Based upon the findings, the carbamazepine dose may need to be reduced by 25 % to 50 % in the presence of **VUNAD**/rtv.

Antimalarials

An interaction trial between darunavir/rtv (100 mg twice daily) and artemether/lumefantrine (80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours) showed an increase in exposure to lumefantrine by 2,75-fold, while exposure to darunavir was not affected. The exposure to artemether and its active metabolite, dihydroartemisinin, decreased by 16 % and 18 %, respectively. The combination of **VUNAD** and artemether/lumefantrine can be used without dose adjustments; however, due to the increase in

lumefantrine exposure, the combination should be used with caution.

Colchicine

Concomitant use of colchicine and **VUNAD**/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout flares in patients on **VUNAD**/rtv, the recommended dose of colchicine is 0,5 mg (1 tablet), followed by 0,25 mg 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout flares in patients on **VUNAD**/rtv, the recommended dose of colchicine is 0,25 mg every day or every other day. For the treatment of familial Mediterranean fever in patients on **VUNAD**/rtv, the maximum dose of colchicine is 0,5 mg every day (may be given as 0,25 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with **VUNAD**/rtv.

Antihistamines (Astemizole)

Exposure to these antihistamines may be increased when co-administered with **VUNAD**/rtv. Concomitant use of VUNAD/rtv with astemizole is contraindicated (see Section 4.3).

Calcium channel blockers

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

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

Bosentan is metabolised by cytochrome CYP3A4 and CYP2C9. Concomitant use of bosentan and **VUNAD** should be avoided (see section 4.3).

Fluticasone

Concomitant use of inhaled fluticasone and **VUNAD**/rtv may increase plasma concentrations of fluticasone. Alternatives should be considered, particularly for long term use.

Hepatitis C virus (HCV) direct-acting antivirals:

NS3-4A protease inhibitors

Boceprevir

In an interaction trial between darunavir/rtv (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 **VUNAD**/rtv with boceprevir (see section 4.3).

Telaprevir

In an interaction trial between darunavir/rtv (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 **VUNAD**/rtv with telaprevir (see section 4.3).

HMG CoA reductase inhibitors

HMG CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with **VUNAD** /rtv. Increased concentrations of HMG CoA reductase inhibitors may cause

myopathy, including rhabdomyolysis. Concomitant use of **VUNAD**/rtv with lovastatin and simvastatin is therefore not recommended (see section 4.3).

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, which is only 15 % lower than that obtained with atorvastatin (40 mg once daily) alone. When administration of atorvastatin and **VUNAD**/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 (100 mg twice daily) increased exposure to a single dose of pravastatin (40 mg) by approximately 80 %, but only in a subset of subjects. When administration of pravastatin and **VUNAD**/rtv is required, it is recommended to start with the lowest possible
dose of pravastatin and titrate up to the desired clinical effects while monitoring safety (see section 4.4).

An interaction study evaluating darunavir/rtv (100 mg
twice daily) in combination with rosuvastatin (10 mg once daily) resulted in a 50 % increase in rosuvastatin exposure. It is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for
safety.

H2 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 once daily) did not affect the exposure to darunavir. Based on these results, **VUNAD**/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 **VUNAD**/rtv is not recommended. The combination may result in 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 **VUNAD**/rtv. Therapeutic drug monitoring of the immunosuppressive agent is recommended when co-administered with **VUNAD**/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 **VUNAD**/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by **VUNAD**/rtv. This was confirmed in an interaction trial where 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 **VUNAD** is contraindicated (see section 4.3).

Methadone

An interaction trial investigating the effect of darunavir/rtv (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 **VUNAD**/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients (see section 4.4).

Buprenorphine/naloxone

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

Oestrogen based contraceptives

The results of an interaction trial between darunavir/rtv (100 mg twice daily) and ethinylestradiol and

norethindrone 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 4.4).

PDE-5 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 PDE-5 inhibitors for the treatment of erectile dysfunction with **VUNAD**/rtv should be done with caution. If concomitant use of **VUNAD**/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 dose in 72 hours or tadalafil at a single dose not exceeding 10 mg dose in 72 hours is recommended (see section 4.4).

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, coadministration of **VUNAD**/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 **VUNAD**/rtv, a dose adjustment for tadalafil is warranted. In patients who have been receiving **VUNAD**/rtv for at least 1 week, start tadalafil at 20 mg, once daily and increase to 40 mg once daily based upon individual tolerability. For patients on tadalafil and initiating **VUNAD**/rtv, discontinue the use of tadalafil at least 24 hours prior to initiating **VUNAD**/rtv and avoid the use of tadalafil during the initiation of **VUNAD**/rtv. After at least 1 week following the initiation of **VUNAD**/rtv, resume tadalafil at 20 mg once daily and increase to 40 mg once daily based upon individual tolerability.

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/rtv (100 mg twice daily) was administered with rifabutin (150 mg once every other day). Based on the safety profile of **VUNAD**/rtv, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for **VUNAD**/rtv. The exposure to rifabutin (sum of main compound 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 **VUNAD** and ritonavir (see section 4.3).

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 **VUNAD/**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 **VUNAD**/rtv should be monitored for antidepressant response.

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.

Breastfeeding:

It is not known whether darunavir is excreted in human milk.

Studies in rats have demonstrate 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 **VUNAD**

Fertility:

No human data on the effect of darunavir on fertility are available.

4.7 Effects on ability to drive and use machines

VUNAD in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing **VUNAD** co-administered with cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile:

Side effects are tabulated in order of frequent, less frequent and frequency unknown.

Tabulated summary of adverse reactions:

Organ system/ disorder	**Frequent**	**Less frequent**	**Frequency unknow**
Infections and infestations	---	Herpes simplex	---
Blood and lymphatic system disorders	---	Thrombocy-topenia, neutropenia, anaemia, leukopenia, increased eosinophil count	---
Immune system disorders	---	immune reconstitution inflammatory syndrome, (drug) hypersensitivity	---
Endocrine disorders	---	hypothyroidism, increased blood thyroid stimulating hormone	---
Metabolism and nutrition disorders	hyper- triglyceride-aemia, hyper-cholesterol-aemia,	Diabetes mellitus, gout, anorexia, dyslipidaemia, lipodystrophy, decreased appetite, decreased weight,	---

	hyperlipidaemia, hyperglycaemia,	increased weight, insulin resistance, decreased high density lipoprotein, increased appetite, polydipsia, increased blood lactate dehydrogenase	
Psychiatric disorders	insomnia	depression, disorientation, anxiety, sleep disorder, abnormal dreams, nightmare, decreased libido, confusional state, altered mood, restlessness	---
Nervous system disorders	headache, peripheral neuropathy, dizziness	lethargy, paraesthesia, hypo-aesthesia, dysgeusia, disturbance in attention, memory impairment, somnolence, syncope, convulsion, ageusia, sleep phase rhythm- disturbance	---
Eye disorders	---	conjunctival hyperaemia, dry eye, visual disturbance	---
Ear and labyrinth disorders	---	vertigo	---
Cardiac disorders	---	myocardial infarction, angina pectoris, prolonged electro - cardiogram QT, tachycardia, acute myocardial infarction, sinus bradycardia, palpitations	---
Vascular disorders	---	hypertension, flushing	---
Respiratory, thoracic and mediastinal disorders	---	dyspnoea, cough, epistaxis, throat irritation, rhinorrhoea	---
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, abdominal pain, increased blood	Dyspepsia, flatulence, pancreatitis, gastritis, gastro-oesophageal reflux disease, aphthous stomatitis, retching,	---

	amylase, , abdominal distension, flatulence	dry mouth, abdominal discomfort, constipation, increased lipase, eructation, oral dysaesthesia, stomatitis, haemat -emesis, cheilitis, dry lip, coated tongue	
Hepatobiliary disorders	increased alanine aminotransferase	hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased trans -aminase, increased aspartate amino -transferase, increased blood bilirubin, increased blood alkaline phosphatase, increased gamma-gluta- myl - transferase	---
Skin and subcutaneous tissue disorders	rash (including macular, maculopapular, papular, erythematous and pruritic rash)	angioedema, generalised rash, allergic dermatitis, urticaria, eczema, erythema, hyperhidrosis, night sweats, alopecia, acne, dry skin, nail pigmentation, DRESS, Stevens-Johnson syndrome, erythema multiforme, dermatitis, seborrhoeic dermatitis, skin lesion, xeroderma, pruritus	toxic epidermal necrolysis, acute generalised exan -thematous pustulosi
Musculoskeletal and connective tissue	---	myalgia, osteonecrosis, muscle spasms, muscular	---

disorders		weakness, arthralgia, pain in extremity, osteoporosis, increased blood creatine phosphor kinase, Musculo skeletal stiffness, arthritis, joint stiffness	
Renal and urinary disorders	---	acute renal failure, renal failure, nephrolithiasis, increased blood creatinine, proteinuria, bilirubinuria, dysuria, nocturia, pollakiuria, decreased creatinine renal clearance	---
Reproductive system and breast disorders	---	erectile dysfunction, gynaecomastia	---
General disorders and administration site conditions		pyrexia, chest pain, peripheral oedema, malaise, feeling hot, irritability, pain, chills, abnormal feeling, xerosis, asthenia, fatigue	---

Description of selected adverse reactions:

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has also been associated with metabolic abnormalities such as

hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

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

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

In patients co-infected with hepatitis B or C virus receiving **VUNAD/**rtv, the incidence of adverse events and clinical chemistry abnormalities were not higher than in patients receiving **VUNAD**/rtv who were not co-infected, except for increased hepatic enzymes (see section 4.4). The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection.

4.9 Overdose

Human experience of acute overdose with **VUNAD**/rtv is limited.

There is no specific antidote for overdose with **VUNAD**. Treatment of overdose with **VUNAD** 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

A.20.2.8 Antiviral agents.

5.1 Pharmacodynamic properties

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 EC50 values ranging from 1,2 to 8,5 nM (0,7 to 5,0 ng/ml).

The EC50 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 etravirine, nevirapine, delavirdine, or efavirenz and the fusion inhibitor enfuvirtide. No antagonism was observed between darunavir and any of those antiretrovirals.

Resistance in *vitro*

In vitro darunavir-resistant virus isolates from wildtype HIV-1 selected viruses showing decreased susceptibility to darunavir (range: 6-21-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: 53 641-fold change in EC50 values) from 9 HIV-1 strains harbouring multiple PI (protease inhibitor) resistance-associated mutations (RAMs) 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 9 darunavir resistant isolates. A minimum of 8 of these darunavir in vitro selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (fold change [FC] > 10) to darunavir.

In 1 113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir and in 886 baseline isolates from the patients enrolled in clinical trials, only

the subgroups with > 10 PI RAMs 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 resistant to at least one protease inhibitor. Seven of the nine darunavir resistant viruses selected from PI resistant viruses had phenotypic data for tipranavir. Six of those showed a fold change (FC) < 3 for tipranavir, indicative of cross-resistance between these 2 protease inhibitors.

Cross-resistance between darunavir and the nucleoside /nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors, the entry inhibitors, or the integrase 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 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 was rapidly 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 a single dose of darunavir alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily 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 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 cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, darunavir tablets should be taken with cobicistat or 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.

Biotransformation:

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 isozymeCYP3A4. A

14C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single400/100 mg darunavir with ritonavir dose was due to the parent active substance. At least 3 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 14C-darunavir with ritonavir dose, approximately 79.5% and 13.9% of the administered dose of

14C-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.

Characteristics in specific groups of subjects or patients:

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 (see section 4.4).

Gender

Population pharmacokinetic analysis showed a slightly higher darunavir exposure 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 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 (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) and moderate (Child Pugh Class B, n=8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see section 4.2 and 4.4).

Paediatric population:

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

5.3 Preclinical safety data

No information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dry mix:

Darunavir Amorphous (Active ingredient)

Silica, colloidal anhydrous (grade 200)

Wet Granulation:

Silica, colloidal anhydrous (grade 200)

Purified Water

Extra Granulation:

Silicified microcrystalline cellulose

Silica, colloidal anhydrous (grade 200)

Crospovidone

Lubrication:

Magnesium stearate

Film Coating:

Opadry II Yellow 85F520012

Purified Water

6.2 Incompatibilities

N/A

6.3 Shelf life

- Blister pack:

Shelf-life: 24 months

- HDPE Container:

Shelf-life: 24 months

- Bulk Pack:

Shelf-life: 12 months

6.4 Special precautions for storage

Store below 25°C

Keep the bottle tightly closed.

Keep in original container packaging until required for use.

KEEP OUT OF SIGHT AND REACH OF CHILDREN.

6.5 Nature and contents of container

Darunavir Tablets 400 mg:

60's & 56's Count HDPE Container.

10 x 10's Alu-Alu Blister Pack.

500's Stimulated Bulk pack.

Darunavir Tablets 800 mg:

60's & 56's Count HDPE Container.

10 x 10's Alu-Alu Blister Pack.

500's Stimulated Bulk pack.

Not all pack sizes might be marketed.

6.6 Special precautions for disposal <and other handling

N/A

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate

Campus, Building No.2,

First Floor, 74 Waterfall Drive, Midrand, 2066

Telephone number: 012 644 1220

Fax number: 012 644 1564

e-mail address: nokuthula.n@heterodrugs.com

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