Applicant/PHRC: ***Hetero Drugs South Africa (Pty) Ltd***

Product proprietary name: ***TONATADIN 400/50***

Dosage form and strength: ***Film coated tablet and 400 /50 mg***

FINAL PROFESSIONAL INFORMATION FOR TONATADIN

WARNING:

CO-ADMINISTRATION OF TONATADIN WITH CERTAIN NON-SEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTI-DYSRHYTHMICS OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF TONATADIN ON THE HEPATIC METABOLISM OF THESE MEDICINES. SEE SECTIONS 4.3 AND 4.4.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TONATADIN 400/50 (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of TONATADIN contains darunavir ethanolate equivalent to 400 mg of darunavir and ritonavir USP 50 mg.

Contains no sugar.

'for full list of excipients, see section 6.1'

3 PHARMACEUTICAL FORM

Yellow, capsule shaped, bevel edged and biconvex film coated tablets debossed with 'H' on one side and 'D8' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TONATADIN, in combination 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 TONATADIN.

There is no information on the use of TONATADIN in the paediatric population for the once daily dose.

4.2 Posology and method of administration

TONATADIN must always be given in combination with other antiretroviral medicines.

Posology

Adults:

Genotypic or phenotypic testing should guide the use of TONATADIN. TONATADIN 800/100 mg (two tablets) once daily dosing regimen is recommended in HIV protease- inhibitor-naïve patients and in treatment-experienced patients with demonstrated absence of DRV-RAMs. The ritonavir included in the formulation is used as a pharmacokinetic enhancer of darunavir (see Sections 4.5 and 5.2).

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 TONATADIN in paediatric patients have not been established.

Missed Dose(s):

In case a dose of TONATADIN was missed within 12 hours of the time it is usually

taken, patients should be instructed to take the prescribed dose of TONATADIN with food as soon as possible. If this was noticed later than12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Hepatic impairment:

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

Method of administration

Orally.

TONATADIN should be taken with food. The type of food does not affect the exposure to TONATADIN.

4.3 Contraindications

Hypersensitivity to darunavir or ritonavir or to any of the excipients of TONATADIN

(listed in section 6.1).

Darunavir and ritonavir are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. TONATADIN should not be co-administered with medicines that are 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 TONATADIN	
Medicine Class: Medicine Name	Clinical Comment
Anticonvulsants: Phenobarbitone Phenytoin	Phenobarbitone and phenytoin are inducers of CYP450 enzymes. TONATADIN should not be used in combination with phenobarbitone, or phenytoin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may

	result in loss of therapeutic effect to TONATADIN (see section 4.5).
Antihistamines: Astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmia.
Antimycobacterial: Rifampicin	Rifampicin is a potent inducer of CYP450 metabolism. TONATADIN should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to TONATADIN (see section 4.5).
Rifabutin	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 TONATADIN (see section 4.5).
Endothelin receptor antagonist: Bosentan	Concomitant use of bosentan and TONATADIN shoud be avoided (see section 4.5).
PDE-5 inhibitor: Sildenafil – when intended for the 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).
Antigout: Colchicine in patients with hepatic or renal impairment	Co-administration of TONATADIN 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:	CONTRAINDICATED due to potential for serious and/or life-

Dihydroergotamine Ergonovine Ergotamine Methylergonovine	threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agents: 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	It is not recommended to co-administer TONATADIN with boceprevir or telaprevir (see section 4.5).
Herbal Products: St. John's wort (*Hypericum perforatum*)	TONATADIN should not be used concomitantly with products containing St. John's wort (Hypericum perforatum) because coadministration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to TONATADIN (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	CONTRAINDICATED because concomitant systemic use of ketoconazole, itraconazole or voriconazole and TONATADIN may

Itraconazole Voriconazole	increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by TONATADIN, while the plasma concentrations of voriconazole may be decreased in the presence of TONATADIN (see section 4.5).
Buprenorphine/ naloxone	The results of an interaction trial with TONATADIN and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when buprenorphine/naloxone was administered with TONATADIN. Exposure of the active metabolite, norbuprenorphine, increased by 46 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if TONATADIN and buprenorphine are co-administered (see section 4.5).
Antidysrhythmics: Amiodarone Bepridil Flecainide Propafenone Quinidine Encainide Digoxin	CONTRAINDICATED with TONATADIN due to potential cardiac dysrhythmias.
Antipsychotic: Blonanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonanserin.
Long-acting beta-adrenoceptor agonist: Salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.

4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy, including TONATADIN, 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 TONATADIN in patients aged 65 and over, caution should be exercised in the administration of TONATADIN in elderly patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see section 5.2).

General

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

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. TONATADIN 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 TONATADIN. The discontinuation rate due to rash in patients using TONATADIN was 0,5 %.

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

Sulpha allergy

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

Patients with coexisting conditions

Hepatic impairment

TONATADIN 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 5.2).

Hepatotoxicity

Medicine-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with

TONATADIN. 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 TONATADIN 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 pretreatment elevations of transaminases, especially during the first several months of TONATADIN 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 TONATADIN 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 TONATADIN 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 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 protease inhibitors such as TONATADIN. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has been postulated, although a mechanism of action has not been established. Haemophilia patients should therefore be made aware of the possibility of increased bleeding.

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 protease inhibitor therapy such as TONATADIN. Some patients required either initiation or dose adjustment of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis has occurred. Patients who discontinued protease inhibitor therapy, the hyperglycaemia persisted in some cases.

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 TONATADIN 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

Darunavir and ritonavir are both inhibitors of CYP3A. Co- administration of [PRODUCT

NAME] 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 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 TONATADIN. This can lead to prolongation or increase of their therapeutic effect and adverse events (see section 4.5).

HMG-CoA Reductase Inhibitors

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on
CYP3A for metabolism, thus concomitant use of TONATADIN with simvastatin or
lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis. Caution must be exercised and reduced doses should be considered if TONATADIN is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A4. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with TONATADIN co-administration. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see TABLE 2).

Methadone

No adjustment of methadone dosage is required when initiating co-administration of
TONATADIN. 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

Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction or pulmonary hypertension in patients receiving TONATADIN. Co-administration of TONATADIN with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as hypotension and prolonged erection. Concomitant use of sildenafil with TONATADIN is contraindicated in pulmonary arterial hypertension patients (see section 4.3 and 4.5).

Ritonavir

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

Corticosteroids

Concomitant use of RITONAVIR and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations.

Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when RITONAVIR has been co-administered with inhaled or intranasally administered fluticasone propionate. Similar findings with concomitant administration of RITONAVIR and other inhaled corticosteroids that are metabolised similarly to fluticasone, such as budesonide, cannot be excluded. Particular caution should

be used when administering RITONAVIR and any of these inhaled or intranasally administered glucorticoids (see section 4.5).

Herbal Products

Patients on RITONAVIR should not use products containing St. John's Wort (Hypericum perforatum) because co-administration may be expected to reduce plasma concentrations of ritonavir. This may result in loss of

therapeutic effect and development of resistance (see section 4.3 and 4.4).

Resistance/Cross-Resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of RITONAVIR therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect RITONAVIR therapy will have on the activity of concordantly or subsequently administered protease inhibitors.

Laboratory Tests

RITONAVIR has been associated with alterations in triglycerides, ALT, AST, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating RITONAVIR therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information concerning laboratory test alterations associated with nucleoside analogues, medical practitioner should refer to the complete product information for each of these medicines.

PR Interval Prolongation

Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Reports of second or third degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in

patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving RITONAVIR.RITONAVIR should be

used with caution in such patients.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump),

peripheral wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving protease inhibitors.

Lipid Disorders

Treatment with RITONAVIR therapy in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride

and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See TABLE 2 for additional information on potential medicine interactions with RITONAVIR and HMG-CoA Reductase Inhibitors (hypolipidemics).

4.5 Interaction with other medicines and other forms of interaction

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

TONATADIN 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.

TONATADIN 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. TONATADIN 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 TONATADIN (see section 4.3 and 4.5).

TONATADIN should not be used concomitantly with products containing St. John's Wort (*Hypericum perforatum*)

because co-administration may cause significant decreases in darunavir and ritonavir plasma concentrations. This may result in loss of therapeutic effect to TONATADIN (see section 4.3 and 4.4).

Antiretroviral medicines

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

Didanosine

TONATADIN (600/100 mg twice daily) did not significantly affect didanosine exposure. The combination of TONATADIN and didanosine can be used without dose adjustments. As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered1 hour before or 2 hours after TONATADIN (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 TONATADIN (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 darunavir, ritonavir, or tenofovir disoproxil fumarate are required when these medicines are co-administered.

Other NRTIs

Based on the different elimination pathways of other NRTSs such as zidovudine, zalcitabine emtricitabine, stavudine, lamivudine and abacavir that are primarily renally excreted, no medicine interactions are expected for these medicines and TONATADIN.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine

In an interaction trial between TONATADIN (600/100 mg twice daily) and etravirine,

there was a 37 % decrease in etravirine exposure in the presence of TONATADIN and no relevant change in exposure to darunavir. Therefore, TONATADIN can be co-administered with etravirine 200 mg twice daily without dose adjustments.

Efavirenz

An interaction trial between TONATADIN (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 TONATADIN. The combination of TONATADIN and efavirenz should be used with caution.

Nevirapine

The results of an interaction trial with [PORODUCT NAME] 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 TONATADIN. Since this difference is not considered to be clinically relevant, the combination of TONATADIN and nevirapine can be used without dose adjustments.

Rilpivirine

In an interaction trial between TONATADIN (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 TONATADIN. Since this difference is not considered to be clinically relevant, the combination of TONATADIN and rilpivirine can be used without dose adjustments.

<u>HIV protease inhibitors</u> (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 was given orally in combination with ritonavir at

100 mg twice daily. Therefore, darunavir 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 (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 TONATADIN 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 TONATADIN. It is not recommended to combine saquinavir and darunavir, with or without low dose ritonavir.

Atazanavir

An interaction trial between TONATADIN (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

TONATADIN.

Indinavir

In an interaction trial between TONATADIN (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 TONATADIN.

Other HIV protease inhibitors

The co-administration of TONATADIN 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 TONATADIN, the dose of maraviroc should be 150 mg twice daily. An interaction trial between TONATADIN (600/100 mg twice daily) and maraviroc (150 mg twice daily) demonstrated that in the presence of TONATADIN 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 TONATADIN.

Concomitant use of TONATADIN 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 TONATADIN. Caution is warranted and therapeutic medicine monitoring of antidysrhythmics is recommended when darunavir is administered with antidysrhythmic medicines.

Digoxin

An interaction trial with TONATADIN (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 TONATADIN. Serum digoxin concentrations should be monitored to assist in the titration.

Anticoagulants

Warfarin concentrations may be affected (decreased) when co- administered with TONATADIN. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with [PPRODUCT NAME].

Anticonvulsants (phenobarbitone, phenytoin and carbamazepine)

Phenobarbitone and phenytoin

Phenobarbitone and phenytoin are inducers of CYP450 enzymes. TONATADIN 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 darunavir (see section 4.3).

Carbamazepine

An interaction trial between TONATADIN (600/100 mg twice daily) and carbamazepine (200 mg twice daily) showed that the exposure to darunavir, co-administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC_{12h}) was decreased by 49 %. For carbamazepine, AUC_{12h} was increased by 45 %. No dose adjustment for TONATADIN is recommended. If there is a need to combine TONATADIN 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 TONATADIN.

Antimalarials

An interaction trial between TONATADIN (600/100 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 darunavir 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 TONATADIN may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout flares in patients on TONATADIN, 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 TONATADIN, 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 TONATADIN, the maximum dose of colchicine is0,5 mg every day (may be given as0,25 mg twice daily). Patients with renal or hepatic impairment should not be given colchicine with TONATADIN.

Antihistamines (Astemizole)

Exposure to these antihistamines may be increased when co- administered with TONATADIN. Concomitant use of TONATADIN 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 TONATADIN are used concomitantly. Caution is warranted and careful clinical monitoring is recommended.

Clarithromycin

An interaction trial between TONATADIN (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 patients with CLcr of 30 to 60 ml/min, the dose of clarithromycin should be reduced by 50 %.

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

Dexamethasone

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 darunavir should be avoided (see section 4.3).

Fluticasone

Concomitant use of inhaled fluticasone and TONATADIN 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 TONATADIN (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 TONATADIN with boceprevir (see section 4.3).

Telaprevir

In an interaction trial between TONATADIN (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 TONATADIN 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 TONATADIN. Increased concentrations of HMG CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of TONATADIN 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 TONATADIN (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 TONATADIN 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.

TONATADIN (600/100 mg twice daily) increased exposure to a single dose of pravastatin (40 mg) by approximately 80 %, but only in a subset of patients. When administration of pravastatin and TONATADIN is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired monitoring safety (see section 4.4). An interaction study evaluating TONATADIN (600/100 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.

<u>H_2 Receptor antagonists and proton pump inhibitors</u>

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

<u>Inhaled beta agonist (salmeterol)</u>

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

<u>Immunosuppressants (ciclosporin, tacrolimus, sirolimus)</u>

Exposure to ciclosporin, tacrolimus, or sirolimus may be increased when co-administered with TONATADIN. Therapeutic drug monitoring of the immunosuppressive agent is recommended when co-administered with TONATADIN.

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 TONATADIN may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by TONATADIN. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg twice daily) with TONATADIN (400/100 mg twice daily) increased exposure of ketoconazole and darunavir by 212 % and 42 %, respectively. Concomitant use of ketoconazole, itraconazole and voriconazole with darunavir is contraindicated (see section 4.3).

Methadone

An interaction trial investigating the effect of TONATADIN (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 TONATADIN. 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 TONATADIN and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with TONATADIN. Exposure of the active metabolite, norbuprenorphine, increased by 4 %. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if TONATADIN and buprenorphine are co-administered.

Oestrogen based contraceptives

The results of an interaction trial between TONATADIN (600/100 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 TONATADIN (400/100 mg twice daily). Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with TONATADIN should be done with caution. If concomitant use of TONATADIN 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 72hours 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 TONATADIN 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 TONATADIN, a dose adjustment for tadalafil is warranted. In patients who have been receiving TONATADIN 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 TONATADIN, discontinue the use of tadalafil at least 24 hours prior to initiating TONATADIN and avoid the use use of tadalafil during the initiation of TONATADIN. After at least 1 week following the initiation of TONATADIN, 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 TONATADIN (600/100 mg twice daily) was administered with rifabutin (150 mg once every other day). Based on the safety profile of TONATADIN, the increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for TONATADIN. 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 darunavir 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 TONATADIN (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 TONATADIN. If SSRIs are co-administered with TONATADIN, 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 TONATADIN should be monitored for antidepressant response.

Ritonavir

Medicines which increase CYP3A activity (e.g. phenobarbitone, carbamazepine, dexamethasone, phenytoin, rifampicin and rifabutin) would be expected to increase the clearance of ritonavir resulting in decreased ritonavir plasma concentrations.

RITONAVIR has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2,
CYP2E1. There is evidence that RITONAVIR may induce glucuronosyl transferase, CYP1A2, CYP2C9 and CYP2C19 enzymes. Decreased plasma concentrations of the other
medicine and loss of therapeutic effects during RITONAVIR co-administration may signify the may signify the need for dosage alteration of these medicines.

In addition to the medicines listed in the section 4.3, TABLE 2 summarises some commonly prescribed medicines, separated by the type of metabolism and expected magnitude of interaction when co-administered with ritonavir. Co-administration of RITONAVIR and medicines primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicine, which could increase or prolong its therapeutic and adverse effects.

Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir. Dosage reductions may be required for those medicines extensively metabolised by CYP3A.

Cardiac and neurologic events have been reported when RITONAVIR has been co-administered with disopyramide, mexiletine, nefazodone or fluoxetine. The possibility of interaction cannot be excluded.

Table 2:

Potential effects on medicines co-administered with RITONAVIR.

(Contraindicated Medications are listed in Column 1)

Medicine Category	**Representative Medicines by Potential Interaction Category**					
	Contraindicated Medication	Large[1] ↑ AUC[2] (CYP3A)	Moderate[1] ↑ AUC[2] (CYP2D6)	Moderate[1] ↑ or ↓ AUC[2] (CYP2C9/19)	Possible ↓ AUC[2] (Unknown CYP)	Possible ↓ AUC[2] (Glucuronidation)
Analgesics, narcotics		Alfentanil	Hydrocodone		Levamethadyl	Codeine Hydromorphone

		Fentanyl	Oxycodone Tramadol		(LAAM)	Meperidine* Methadone* Morphine
Analgesics, non-steroidal				Diclofenac Flurbiprofen Ibuprofen Indomethacin Piroxicam	Nabumetone Sulindac	Ketoprofen Ketorolac Naproxen
Antidysrhythmic	Amiodarone Encainide Flecainide Propafenone Quinidine Digoxin	Lidocaine	Disopyramide Mexiletine		Tocainide[11]	
Antiasthmatic						Theophylline*
Antibiotic, macrolide		Erythromycin	Clarithromycin*			
Antibiotic, steroidal		Fusidic acid				
Anticovuls		Carbam	Clonaze		Phenob	Divalproex

ant		azepine	pam Ethosuximide		arbitone	Lamotrigine Phenytoin
Antidepressant tricyclic			Amitriptyline Clomipramine Desipramine* Imipramine Maprotiline Nortriptyline Trimipramine		Doxepin [11]	
AntidepressantSSRIs and non-tricyclics		Nefazodone Sertaline	Fluoxetine Paroxetine Trazodone* Venlafaxine		Fluvoxamine	Bupropion
Antidiarrhoeal						Diphenoxylate Loperamide

Antiemetics **Prokinetics**	Cisapride		Ondansetron		Prochlorperazine [11] Promethazine	Metaclopramide
Antifungal medicines	Voriconzale	Itraconazole Ketoconazole* Miconazole				
Antihistamines	Astemizole	Loratadine				
Antihypertensive		Bosentan		Losartan	Doxazosin [11] Prazosin [11] Terazosin[11]	
Antimyco-bacterial		Rifabutin*			Ethionamide Rifampicin	
Antiparasitics	Quinine			Proguanil	Albendazole Chloroquine Metronid	Atovaquone

					azole Primaquine Pyrimethamine	
Antipsychotics	Blonanserin					
Protein pump inhibitors				Lansoprazole Omeprazole		
B-blockers			Metoprolol Penbutolol Pindolol Timolol	Propranolol	Betaxolol[11]	
β2-agonist (long acting)	Salmeterol					
Calcium channel blockers	Bepridil	Amlodipine Diltiazem Felodipine Isradipine				

		Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Verapamil				
Cancer chemo therapeutic medicines		Tamoxifen	Etoposide Paclitaxel Vinblastine Vincristine	Cyclophosphamide[3] Ifosfamide[3]	Daunorubicin[11] Doxorubicin[11]	
Ergot alkaloids and derivatives	Dihydroergotamine Ergonovine[11] Ergotamine Methylerg	Bromicriptine			Methysergide[11]	

	o-novine[11]					
Haemorheologic agent					Pentoxifylline	
Herbal Products	St. John's Wort					
HIV Antivirals		Atazanavir Darunavir (fos) amprenavir Indinavir* Saquinavir* Tipranavir	Maraviroc		Nevirapine[11]	
Hypo-glycaemics				Glimepiride Glipizide Glyburide Tolbutamide		
Hypolipidemics	Lovastatin Simvastatin	Atorvastatin	Rosuvastatin		Gemfibrozil	Clofibrate

Immuno-suppressants		Ciclosporine Everolimus Tacrolimus Sirolimus (rapamycin)				
Neuroleptics	Pimozide		Chlorpromazine Haloperidol Perphenazine Risperidone			Clozapine
PDE5 inhibitor	Sildenafil indicated for PAH	Sildenafil indicated for ED Tadalafil Vardenafil				
Sedative/hypnotics	Midazolam Triazolam	Buspirone	Clorazepate Diazepa			Lorazepam Oxazepam

			m Estazolam Flurazepam Zolpidem			Propofol Temazepam
Steroids		Dexamethasone Fluticasone*	Prednisone			Ethinyl Estradiol*
Stimulants			Dexfenfluramine Methamphetamine		Methylphenidate	

[1] Large = > 3X; Moderate = 1.5-3X

[2] AUC = area under the plasma concentration-time curve, a measure of medicine exposure.

[3] An increase in the AUC of cyclophosphamide and ifosfamide, both activated by CYP, may correspond to a decrease in the AUC of the active metabolite (s) and a possible decrease in efficacy of these medicines.

[11] A possible increase in concentration is more likely when combined with ritonavir.

*Clinical medicine interaction study has been performed

Alprazolam: Co-administration of alprazolam with RITONAVIR resulted in a statistically significant decrease in mean alprazolam C_{max} values (16 %) but not in mean AUC values (12 %).

Amprenavir: Literature reports have shown that concentrations of the HIV-protease inhibitor, amprenavir are increased when co-administered with RITONAVIR.

Bosentan: Co-administration of bosentan and RITONAVIR may increase steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC). Refer to the bosentan package insert for prescribing information.

Bupropion: Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of RITONAVIR is expected to decrease bupropion levels.

Buspirone: Buspirone is primarily metabolised by CYP3A4. Concurrent administration of buspirone and RITONAVIR is expected to substantially elevate buspirone levels.

Clarithromycin: the concomitant administration of NORVIR 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31 %, C_{min} increased by 182 % and AUC increased by 77 % with essentially complete inhibition of the formation of 14-[R] hydroxy-clarithromycin. No dosage reduction should be necessary in patients with normal renal function. For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50 %. For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75 %. Doses of clarithromycin greater than 1 gram per day should not be co-administered with RITONAVIR.

Delavirdine: Delavirdine is an inhibitor of CYP3A-mediated metabolism. In a published study, concurrent administration of clinical doses of delavirdine 400 mg three times daily with RITONAVIR 600 mg twice daily (n=12 HIV-infected patients) was reported to increase steady-state ritonavir C_{max} AUC by approximately 50 % and C_{min} by about 75 %. Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by RITONAVIR. When used in combination with delavirdine, a dose reduction of

RITONAVIR should be considered.

Desipramine: Co-administration of RITONAVIR with desipramine resulted in a 145 % mean increase in the AUC of desipramine. Dosage reduction of desipramine should be considered in patients taking the combination.

Didanosine: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 600 mg every 12 hours and didanosine (ddl) 200 mg every 12 hours resulted in a reduction of the ddl steady-state C_{max} and AUC of 16 % and 13 %, respectively. In contrast, little if any effect was noted in RITONAVIR pharmacokinetics. Dose alteration of ddl during concomitant RITONAVIR therapy should not be necessary; however, dosing of the two medicines should be separated by 2.5 hours to avoid formulation incompatibility.

Digoxin: A literature report has shown that coadministration of NORVIR (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when coadministration RITONAVIR with digoxin, with appropriate monitoring of serum digoxin levels.

Disulfiram/Metronidazole: RITONAVIR solution and soft gelatine capsules contain ethanol (43 % and 12 % respectively), therefore, concomitant administration of RITONAVIR and disulfiram or medicines with disulfiram-like reactions (e.g.metronidazole) should be avoided.

Efavirenz: In healthy volunteers receiving 500 mg RITONAVIR twice daily with efavirenz 600 mg once daily, the steady state AUC of efavirenz was increased by 21 %. An associated increase in the AUC of NORVIR of 17 % was observed.

Fluticasone propionate: Concomitant use of RITONAVIR and fluticasone propionate may increase

concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use (see section 4.4).

Fusidic acid: Co-administration of RITONAVIR with fusidic acid is expected to significantly increase fusidic acid and ritonavir concentrations in plasma.

Hypericum perforatum **(St. John's Wort):** Patients on RITONAVIR should not concomitantly use products containing St. John's Wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of ritonavir. This effect may be due to induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see section 4.3 and 4.4).

Indinavir: RITONAVIR inhibits the CYP3A-mediated metabolism of indinavir. In healthy patients, 200 to 400 mg of RITONAVIR twice daily given with a single 400 mg to 600 mg indinavir dose increased the indinavir AUC by 185 to 475 %, C_{max} 21 % to 110 % and C_{min} 11 to 33-fold, relative to 400 and 600 mg indinavir given alone. Concomitant administration of 400 mg RITONAVIR and 400 mg of indinavir twice daily with a meal yielded a similar indinavir AUC, a 4-fold increase in C_{min} and a 50 to 60 % decrease in C_{max} as compared to those resulting from administration of indinavir 800 mg three times daily under fasting conditions. Co-administration of RITONAVIR with indinavir will result in increased indinavir serum concentrations. There is limited safety or efficacy data available on the use of this

combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with RITONAVIR. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole: Concomitant administration of RITONAVIR (500 mg q12h) and ketoconazole (200 mg q6h) resulted in an increase of mean ketoconazole AUC24 and C_{max} by 244 % and 55 %, respectively. The mean half-

life of ketoconazole increased from 2.7 to 13.2 h. Mean AUC_{24} and Cmax of ritonavir increased by 18 and 10 % respectivley. No dosage adjustment of RITONAVIR is necessary; however, doses of ketoconazole 200 mg/day or greater should be used with caution in combination with RITONAVIR and a decreased dosage may be considered.

Methadone: Coadministration of RITONAVIR with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered.

Nelfinavir: Interactions between RITONAVIR and nelfinavir are likely to involve both cytochrome P450 inhibition and induction. Concurrent RITONAVIR 400 mg twice daily significantly increases the concentrations of M8 (the major active metabolite of nelfinavir) and results in a smaller increase in nelfinavir concentrations. In a study in ten patients nelfinavir 750 mg and RITONAVIR 400 mg twice daily yielded slightly higher nelfinavir AUC (160 %), C_{max} (121 %) and C_{trough} (123 %) than historical data for nelfinavir 750 mg three times daily monotherapy. The AUC of M8 was increased by 347 %.

Oral contraceptive, patch contraceptive or implants: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 500 mg every 12 hours and a fixed-combination oral contraceptive resulted in reductions of the ethinyl estradiol mean C_{max} and mean AUC by 32 % and 40 %, respectively. Increased doses of oral contraceptives or patch contraceptives containing ethinyl estradiol, or alternate methods of contraception, should be considered.

Rifabutin: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 500 mg every 12 hours and rifabutin resulted in an approximate 4-fold and 35-fold increase in the AUC of rifabutin and its active metabolite 25-O-deacetyl rifabutin, respectively. The significance of this interaction has been confirmed in clinical trials. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is

recommended (e.g., 150 mg every other day or three times a week). Further dosage reduction may be necessary.

Saquinavir: A pharmacokinetic study demonstrated that RITONAVIR extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. Following approximately four weeks of a combination regimen of saquinavir (400 or 600 mg twice a day) and RITONAVIR (400 or 600 mg twice a day) in HIV-infected patients, saquinavir AUC values were at least 17-fold greater than historical AUC values from patients who received saquinavir 600 mg three times a day without RITONAVIR. When used in combination therapy for up to 24 weeks, doses greater than 400 mg twice a day of either RITONAVIR or saquinavir were associated with an increase in adverse events.

Sildenafil, Tadalafil & Vardenafil: Caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving RITONAVIR. Co-administration of NORVIR with these medicines is expected to increase their concentrations and may result in increased associated adverse events, such as hypotension and prolonged erection. Concomitant use of sildenafil with RITONAVIR is contraindicated in pulmonary arterial hypertension patients (see section 4.3).

Sulfamethoxazole/trimethoprim: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 500 mg every 12 hours and sulfamethoxazole/trimethoprim resulted in a 20 % reduction of the sulfamethoxazole AUC and a 20 % increase of the trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.

Theophylline: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 500 mg every 12 hours and theophylline resulted in a 43 % decrease in the AUC of theophylline. An increased dosage of theophylline may be required.

Tobacco: Tobacco use is associated with an 18 % decrease in the AUC of RITONAVIR.

Trazodone: Concomitant use of RITONAVIR and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as RITONAVIR, the combination should be used with caution and a lower dose of trazodone should be considered.

Vincristine, Vinblastine: Serum concentrations may be increased when coadministered with RITONAVIR resulting in the potential for increased incidence of adverse events.

Voriconazole: A study has shown that co-administration of RITONAVIR 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82 %; therefore, co-administration of these medicines are contraindicated (see section 4.3).

Warfarin: Anticoagulant metabolism may be induced, resulting in decreased concentrations of warfarin.

Zidovudine: A pharmacokinetic study demonstrated that the concomitant administration of RITONAVIR 300 mg every 6 hours and zidovudine (AZT) 200 mg every 8 hours resulted in a reduction of the zidovudine C_{max} and AUC of 27 % and 25 %, respectively. In contrast, little if any effect was noted on RITONAVIR pharmacokinetics. Dose alteration of AZT during concomitant ritonavir therapy should not be necessary.

Table 3:

Effect on AUC and C_{max} of Co-administration of RITONAVIR with Other Medicines

Medicine	Effects on Ritonavir Ritonavir Dosage	n	AUC % (95 CI)	C_{max} % (95 CI)
Clarithromycin 500 mg every 12 hours 4 days	200 mg every 8 hours 4 days	22	↑ 12 % (2,23 %)	↑ 15 % (2,28 %)
Didanosine 200 mg every 12 hours 4 days	600 mg every 12 hours 4 days	12	↔	↔
Fluconazole 400 mg day 1, 200 mg daily 4 days	200 mg every 6 hours 4 days	8	↑ 12 % (5,20 %)	↑ 15 % (7,22 %)
Fluoxetine 30 mg every 12 hours 8 days	600 mg single dose	16	↑ 19 % (7,34 %)	↔
Rifampicin 600 mg or 300 mg daily 10 days[1]	500 mg every 12 hours 20 days	7,9*	↓ -35 % (7,55 %)	↓ -25 % (-5,46 %)
Zidovudine 200 mg every 8 hours 4 days	300 mg every 6 hours 4 days	10	↔	↔

[1] Preliminary date

↑ Indicates increase

↓ Indicates decrease

↔ Indicates no change

4.6 Fertility, pregnancy and lactation

Pregnancy

TONATADIN is contraindicated in pregnancy and lactation as safety and efficacy have not been demonstrated. Animal studies do not indicate direct harmful effects of darunavir with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Studies with ritonavir indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity.

Breastfeeding

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 TONATADIN.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies of **RITONAVIR** in animal systems have not been completed. **RITONAVIR** was not found to be mutagenic or clastogenic.

4.7 Effects on ability to drive and use machines

No studies on the effects of TONATADIN on the ability to drive or use machines have been performed. However, somnolence and dizziness have been reported in some patients during treatment with regimens containing darunavir and ritonavir, and should be borne in mind when considering a patient's ability to drive or operate machinery.

4.8 Undesirable Effects

Summary of the safety profile

RITONAVIR

The most frequent reported clinical adverse events, other than asthenia, among patients receiving ritonavir were

gastrointestinal and neurological disturbances including nausea, diarrhoea, vomiting, anorexia, abdominal pain, taste perversion and circumoral and peripheral paraesthesias.

Tabulated summary of adverse reactions

Darunavir

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTION**
Immune system disorders	Less frequent	Immune reconstitution syndrome
Metabolism and nutrition disorders	Frequent	Hypercholesterolaemia, hyperglycaemia hyperlipaemia, hypertriglyceridaemia
	Less frequent	Diabetes mellitus, anorexia, dyslipidaemia, lipodystrophy, low density lipoprotein increased
Psychiatric disorders	Less frequent	Abnormal dreams
Nervous system disorders	Frequent	Headache
Gastrointestinal disorders		
	Less frequent	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased, acute pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis acute
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Pruritus, angioedema, Stevens-Johnson Syndrome

Musculoskeletal and connective tissue disorders	Less frequent	Myalgia
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Less frequent	Asthenia, fatigue

RITONAVIR

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTION**
Infections and Infestations	Frequent	Pharyngitis
Blood and lymphatic system disorders	Less frequent	Anaemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocytopenia
Immune system disorders	Frequent	Allergic reaction
Endocrine disorders	Less frequent	Diabetes mellitus
Metabolism and nutrition disorders	Frequent	Anorexia, hyperlipaemia, weight loss, avitaminosis, cachexia, dehydration, oedema, glycosuria, gout, hypercholesterolaemia, peripheral oedema, redistribution/ accumulation of body fat (see section 4.4)

Psychiatric disorders	Frequent	Anxiety, insomnia, agitation, confusion, depression, emotional lability, euphoria, hallucinations, decreased libido, nervousness, personality disorder, abnormal thinking
Nervous system disorders	Frequent	Circumoral paraesthesia, headache, peripheral pareasthesia, taste perversion, dizziness, hyperaesthaesia, paraesthesia, somnolence
	Less frequent	Abnormal dreams, amnesia, aphasia, ataxia, convulsion, grand mal convulsion, inco-ordination, neuralgia, neuropathy, paralysis, parosmia, peripheral neuropathy, peripheral sensory neuropathy, taste loss, tremor, visual field defect
Eye disorders	Frequent	Abnormal vision, amblyopia/blurred vision, blepharitis, diplopia, eye pain, iritis, photophobia, uveitis
Ear and labyrinth disorders	Less frequent	Ear pain, hearing impairment, increased cerumen, tinnitus, vertigo
Cardiac disorders	Less frequent	Palpitations, snycope
Vascular disorders	Frequent	Haemorrhage, hypotension, migraine, peripheral vascular disorder, postural

		hypotention, tachycardia
Respiratory, thoracic and mediastinal disorders	Frequent	Increased cough
	Less frequent	Asthma, dyspnoea, epistaxis, hiccup, hypoventilation, interstitial pneumonia, lung disorder and rhinitis, dry mouth, dyspepsia, eructation, flatulence, local throat irritation, mouth ulcer
Gastrointestinal disorders	Frequent	Abdominal pain, diarrhoea, nausea, vomiting
	Less frequent	Abdomen enlarged, abnormal stools, bloody diarrhoea cheilitis, colitis, constipation, dysphagia, oesophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal haemorrhage, gingivitis, ileitis, oral moniliasis, pancreatitis, periodontal abscess, rectal disorder, tenesmus, thirst
Hepato-biliary disorders	Frequent	Cholangitis, hepatitis, hepatomegaly, liver damage
Skin and subcutaneous tissue disorders	Frequent	Macropapular rash, pruritus, rash, sweating, acne, contact dermatitis, dry skin, eczema, facial oedema, folliculitis, molluscum contagiosum, photosensitivity reaction, psoriasis, seborrhoea, urticaria,

		vesiculobullous rash
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, arthalgia,arthrosis, back pain, facial pain, joint disorder, muscle cramps, muscle weakness,myositis, neck pain, neck rigidity, twitching
Renal and urinary disorders	Frequent	Dysuria, haematuria, kidney calculus, kidney failure kidney pain, nocturia, polyuria, pyelonephritis, urethritis, urinary frequency, urinary retention
Reproductive system and breast disorders	Less frequent	Impotence, penis disorder
General disorders and administration site conditions	Frequent	Asthenia, fever, pain,
	Less frequent	Abnormal gait, chest pain, chills, flu syndrome, malaise, substernal chest pain
Investigations	Frequent	Abnormal liver function tests
	Less frequent	Abnormal electro-oculogram, abnormal electroretinogram, altered hormone level
Injury and poisoning	Less frequent	Accidental injury, hypothermia
Surgical and medical procedures	Frequent	Vasodilation

POST-MARKETING EXPERIENCE

Darunavir

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, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Osteonecrosis

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.

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

In patients co-infected with hepatitis B or C virus receiving TONATADIN, the incidence of adverse events and

clinical chemistry abnormalities were not higher than in patients receiving TONATADIN 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.

RITONAVIR

Nervous system disorders: There have been post-marketing reports of seizure. Cause and effect relationship has not been established.

Metabolism and nutrition disorders: Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope or renal insufficiency has been reported. Syncope, orthostatic hypotension and renal insufficiency have also been reported without known dehydration.

Cardiac disorders: Myocardial infarction has been reported.

Reproductive system and breast disorders: Menorrhagia has been reported.

Reporting suspected adverse reactions after authorisation of TONATADIN is important. It allows continued monitoring of the benefit/risk balance of the TONATADIN. Healthcare professionals are asked to report any suspected adverse to report any suspected adverse reactions to SAHPRA **via the "6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za/publications/Index/8** or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com

4.9 Overdose

Human experience of acute overdose with TONATADIN is limited.

Management of Overdosage:

There is no specific antidote for overdose with TONATADIN. Treatment of overdose

with TONATADIN should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. It is proposed that management of overdose could also entail and administration of activated charcoal. Since TONATADIN is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5 PHARMACOLOGICAL PROPERTIES

CATERGORY AND CLASS: A.20.2.8 Antiviral agents.

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code:

J05AE10.

5.1 Pharmacodynamic properties

Darunavir

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).

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 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 EC_{50} 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.

RITONAVIR

Ritonavir is a peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor and leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.
Ritonavir is used in this combination as pharmacokinetic enhancer, as it is an inhibitor of CYP3A, thereby increasing the plasma concentrations of darunavir.

In vitro data indicate that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of ritonavir that inhibits 50 % and 90 % of viral replication in vitro in plasma-free surroundings is approximately 0,02 µm and 0,11 µm, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines, showed no direct toxicity at concentrations up to 25 µm, with a resulting *in vitro* therapeutic index of at least 1000.

Ritonavir-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to ritonavir and genotypic analysis showed that the resistance was attributable primarily to specific amino acid substitutions in the HIV-1 protease at codons V82F, I84V, A71V and M46I. Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase I/II trials. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at positions 82 (Val to Ala/Phe), 54 (Ile to Val), 71 (Ala to Val/Thr) and 36 (Ile

to Leu), followed by combinations of mutations at an additional 5 specifc amino acid positions. Viral strains isolated in vivo without a change at codon 82 did not have decreased susceptibility to ritonavir. The 82 mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to five-fold decrease in viral sensitivity *in vitro* from baseline. The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established.

The potential for HIV cross-resistance between protease inhibitors has not been fully explored. Therefore, it is unknown what effect ritonavir therapy will have on the activity of concordantly or subsequently administered protease inhibitors. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from five patients were also tested for cross resistance to amprenavir and nelfinavir; isolates from two patients had a decrease in susceptibility to nelfinavir (12 to 14-fold), and none to amprenavir. Cross- resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested *in vitro* retained full susceptibility to ritonavir.

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 patients. The increased exposure to darunavir in HIV-1 infected patients compared to healthy patients 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 metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Absorption

Darunavir was well absorbed following oral administration in the presence of low-dose ritonavir. 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 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 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 14C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg darunavir/rtv dose was due to the parent substance. At least 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/rtv 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.

Special populations

Paediatrics

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

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 ^{14}C-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 (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild (Child-Pugh Class A,) and moderate (Child Pugh Class B) hepatic impairment were comparable with those in healthy patients. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied (see section 4.2 and 4.4).

Ritonavir:

In a pharmacokinetic study in HIV positive fasting subjects, high levels of ritonavir were achieved and maintained for several hours after oral administration of 100 mg, 200 mg, 400 mg, 600 mg, 800 mg or 1 000 mg or ritonavir. Area under the concentration-time curve (AUC) ranged from 3,92 to 123 µg,h/mL, respectively and the maximal concentration (Cmax) ranged from 0,416 to 12,7 µg/mL. The pharmacokinetics of ritonavir was dose-dependent; with more than proportional increases in the AUC and Cmax occurring with increasing dose. The time to maximum concentration (Tmax) remained constant at approximately 2- 4 hours with increasing dose. Renal clearance averaged less than 0,1ℓ/h and was relatively constant throughout the dosage range. There is no parenteral formulation of ritonavir, therefore, the absolute bioavailability has not been determined.

After administration of a single 100 mg dose tablet, the area under concentration-time curve (AUC) is 3,7 µg.h/mL, maximal concentration (Cmax) is 0,44 ± 0,29 µg/mL, Tmax is 4,4 ± 1,2 h.

Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 12 % higher when administered with high fat meal. When the liquid formulation was given under fasting conditions, peak ritonavir concentrations increased 28 %, relative to non-fasting conditions. The clinical implications of these differences are not known.

The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV positive adult volunteers. Upon multiple dosing, ritonavir accumulation is less than predicted from single dose due to a time and dose related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. At steady state with a 600 mg twice day dose, Cmax and Ctrough values of 141,2 and 3,7 µg/mL were observed, respectively.

The t½ of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 6600 mg twice a day has averaged 8,8 ± 3,2 L/h.

No clinically significant differences in AUC or Cmax were noted between males and females. Ritonavir pharmacokinetic parameters were not significantly associated with body weight or lean body mass. The apparent volume if distribution (VD/F) of ritonavir is approximately 0,41 ± 0,25 L/kg after a single dose. The

protein binding of ritonavir in human plasma was noted to be approximately 98 to 99 %. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Total plasma protein binding is constant over the concentration range 1 to 100 µ/mL.

Tissue distribution studies with 14C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios of approximately one measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissue. Ritonavir penetrates minimally into the brain.

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily isozyme CYP3A and to a lesser extent CYP2D6. Animal studies as well as *in vitro* experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Five ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of ritonavir. However, the AUC of the M-2 metabolite was approximately 3 % of the AUC of ritonavir.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86 % of radiolabel was recovered in the stool. In these studies, renal elimination was not found to be major route of elimination of ritonavir.

Effects on electrocardiogram:

QTcF interval was evaluated in placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in healthy adults, with measurements over 12 hours on Day 3. The maximum mean (95 % upper confidence bound) difference in QTcF from placebo was 5,5 (7,6) msec for 400 mg twice daily ritonavir. The Day 3 ritonavir exposure was approximately 1,5-fold higher than that observed with the 600 mg twice-daily dose at steady state. No subject experiences an increase in QTcF of > 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. Maximum PR interval was 252 msec and no second- or third-degree heart block was observed.

Renal impairment:

Currently there is no data specific to this patient population. However, because ritonavir is highly protein bound it is unlikely that ritonavir will be significantly removed by haemodialysis or peritoneal dialysis (see Section 4.2 and 4.4).

Hepatic impairment:

In HIV-infected adult subjects with mild hepatic insufficiency dosed with ritonavir 400 mg twice a day, ritonavir exposures were similar to control subjects dosed with 500 mg twice a day. Results indicated that dose adjustment is not required in patients with mild hepatic impairment. Adequate pharmacokinetic data are not available for patients with moderate hepatic impairment. Protein binding ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function (see Section 4.2, 4.3 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Darunavir Ethanolate
- Ritonavir
- Silicifide microcrystalline cellulose
- Crosprovidone
- Colloidal silicon dioxide
- Magnesium stearate
- Copovidone
- Sorbitan monolaurate
- Dibasic calcium phosphate anhydrous
- Sodium stearyl fumarate

Composition of Opadry yellow 16C82767

- HPMC/Hypromellose 6cP
- Titanium dioxide
- Macrogol/PEG 400
- HPMC/Hypromellose 15cP
- Hydroxypropyl cellulose
- Iron oxide yellow
- Talc
- Macrogol/PEG 3350
- Colloidal anhydrous silica
- Polysorbate 80

6.2. Incompatibilities

N/A

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the tablets in the original container until required for

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

30's count HDPE container

High density polyethylene container 100 cc with 38 mm Neck (heavy weight) with a child resistant plastic caps with pulp liners 38 mm with a desiccant canister 2,0 g, silica gel

56's and 60's count HDPE container

High density polyethylene container 150 cc with 38 mm Neck (heavy weight) with a child resistant plastic caps with pulp liners 38 mm with a desiccant canister 2,0 g, silica gel

120's count HDPE container

High density polyethylene container 300 cc with 53 mm Neck (heavy weight) with a child resistant plastic caps with pulp liners 53 mm with a desiccant canister 2,0 g, silica gel

7 HOLDER OF CERTIFICATE OF REGISTRATION

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10 DATE OF REVISION OF THE TEXT

N/A