SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Tablets 100 mg[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg ritonavir.

Sodium (oral): This medicinal product contains 3.82 mmol (or 87.76 mg) sodium per tablet. To be taken into consideration in patients on a controlled sodium diet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow-coloured, capsule-shaped, film-coated tablets, debossed with "M163" on one side and plain on the other side. No score-line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ritonavir Tablets 100 mg are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older).

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g., those of the WHO).

4.2 Posology and method of administration

Ritonavir Tablets 100 mg should be prescribed by physicians who are experienced in the treatment of HIV infection.

Ritonavir Tablets 100 mg tablets are administered orally and should be ingested with food (see section 5.2).

Ritonavir Tablets 100 mg should be swallowed whole and not chewed, broken or crushed.

Ritonavir dosed as a pharmacokinetic enhancer

When Ritonavir Tablets 100 mg are used as a pharmacokinetic enhancer with other protease inhibitors the Summary of Product Characteristics for the particular protease inhibitor must be consulted.

The following HIV-1 protease inhibitors have been approved for use with ritonavir as a pharmacokinetic enhancer at the noted doses.

Adult use:

Amprenavir 600 mg twice daily with ritonavir 100 mg twice daily
Atazanavir 300 mg once daily with ritonavir 100 mg once daily
Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily
Lopinavir co-formulated with ritonavir (lopinavir/ritonavir) 400 mg/100 mg or 800 mg/200 mg
Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily

[1] Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only

Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily
Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients
Darunavir 800mg once daily with ritonavir 100 mg once daily in ART-naïve patients

Paediatric use: Ritonavir Tablets 100 mg are recommended for children 2 years of age and older. For further dosage recommendations, refer to the product information of other protease inhibitors approved for co-administration with ritonavir. Ritonavir Tablets 100 mg are not recommended in children below 2 years of age due to lack of data on safety and efficacy.

Renal impairment: As ritonavir is primarily metabolised by the liver, it may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency, depending on the specific protease inhibitor with which it is co-administered. However, since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment. For specific dosing information in patients with renal impairment, refer to the Summary of Product Characteristics (SmPC) of the co-administered protease inhibitor.

Hepatic impairment: Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease, (see section 4.3). In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. The SmPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

Elderly: Pharmacokinetic data indicated that no dose adjustment is necessary for elderly patients (see section 5.2).

4.3 Contraindications

Hypersensitivity to ritonavir or to any of the excipients.

Consult the Summary of Product Characteristics of the co-administered drug for other possible contraindications.

Ritonavir Tablets 100 mg should not be given to patients with decompensated liver disease.

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. The following medicines are contraindicated when used with ritonavir and, unless otherwise noted, the contraindication is based on the potential for ritonavir to inhibit metabolism of the co-administered medicinal product, resulting in increased exposure to the co-administered product and risk of clinically significant adverse effects.

The enzyme-modulating effect of ritonavir may be dose dependent.

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased		
α_1-Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 4.5).
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antiarrthymics	Amiodarone, bepridil, encainide, flecanide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecanide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect (see section 4.5)
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterial	Rifabutin	Concomitant use of ritonavir dosed as an antiretroviral agent (600 mg twice daily) and rifabutin is contraindicated due to an increase of rifabutin serum concentrations and risk of adverse reactions including uveitis (see section 4.4). Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted in section 4.5
Antipsychotics/ Neuroleptics	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.

GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.
HMG Co-A Reductase InhibitorLovastatin, simvastatin atorvastatin,rosuvastatin Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see sections 4.4 and 4.5). If co-administered, the lowest initial dose of atorvastatin or rosuvastatin should be used, and the patient should be closely monitored for efficacy and safety. If treatment with an HMG- CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).		
PDE5 inhibitor	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil- associated adverse events (which include hypotension and syncope). See sections 4.4 and 4.5 for coadministration of sildenafil in patients with erectile dysfunction.
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterallyadministered midazolam, see section 4.5.)	

Ritonavir medicinal product level decreased

Herbal Preparation	St. John's Wort	Herbal preparations containing St John's wort (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

Transmission of HIV
Antiretroviral therapy may reduce the risk of sexual transmission of HIV. However, protection is not complete, and patients should continue to take appropriate precautions.

Opportunistic infections
Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection.

When ritonavir is used as a pharmacokinetic enhancer with other PIs, full details on the warnings and precautions relevant to that particular PI should be considered, therefore the Summary of ProductCharacteristics for the particular PI must be consulted.

Patients with chronic diarrhoea or malabsorption: Extra monitoring is recommended when diarrhoea occurs. The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medicinal

products. Serious persistent vomiting and/or diarrhoea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment.

Haemophilia: there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

Diabetes mellitus and hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. A higher risk of lipodystrophy has been associated with stavudine or zidovudine use, older age, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered including the substitution of stavudine by an alternative antiretroviral agent, if feasible (see section 4.8).

Lipid elevations: Treatment with ritonavir has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating therapy with ritonavir and at periodic intervals during therapy. Particular attention should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate.

Pancreatitis: 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 (see section 4.8).

Immune Reactivation Syndrome: in HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymtomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Liver disease: Ritonavir should not be given to patients with decompensated liver disease. For patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation see section 4.2. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be

monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal disease: Since the renal clearance of ritonavir is negligible, decrease in the total body clearance is not expected in patients with renal impairment. For specific dosing information in patients with renal impairment, refer to the Summary of Product Characteristics (SmPC) of the co-administered protease inhibitor. See also section 4.2.

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

PR interval prolongation: Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products 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 (see section 5.1).

Interactions with other medicinal products

The interaction profiles of HIV-protease inhibitors, co-administered with low dose ritonavir, are dependent on the specific co-administered protease inhibitor.

For a description of the mechanisms and potential mechanisms contributing to the interaction profile of the PIs, see section 4.5. Please also review the Summary of Product Characteristics for the particular boosted PI.

Saquinavir: Doses of ritonavir higher than 100 mg twice daily should not be used. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse reactions. Co-administration of saquinavir and ritonavir has led to severe adverse reactions, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.

Saquinavir/ritonavir should not be given together with rifampicin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three medicines are given together (see section 4.5).

Tipranavir: Co-administration of tipranivir with 200 mg of ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.

Fosamprenavir: Co-administration of fosamprenavir with ritonavir in doses greater than 100 mg twice daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended.

Atazanavir: Co-administration of atazanavir with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile ofatazanavir

(cardiac effects, hyperbilirubinemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted. Refer to the atazanavir Summary of Product Characteristics for further details.

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For select medicinal products (e.g., alprazolam) the inhibitory effects of ritonavir on CYP3A4 may decrease over time. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time (e.g., digoxin and fexofenadine - see table "Ritonavir effects on non-antiretroviral medicinal products" below). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect.

Important information regarding medicinal product interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the Summary of Product Characteristics of the co-administered protease inhibitor.

Medicinal products that affect ritonavir levels
Serum levels of ritonavir can be reduced by concomitant use of herbal preparations containing St John's wort (*Hypericum perforatum).* This is due to the induction of medicinal product metabolising enzymes by St John's wort. Herbal preparations containing St John's wort must not be used in combination with ritonavir. If a patient is already taking St John's wort, stop St John's wort and if possible check viral levels. Ritonavir levels may increase on stopping St John's wort. The dose of ritonavir may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's wort (see section 4.3).

Serum levels of ritonavir may be affected by select co-administered medicinal products (eg delavirdine, efavirenz, phenytoin and rifampicin). These interactions are noted in the medicinal product interaction tables below.

Medicinal products that are affected by the use of ritonavir
Interactions between ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in the tables below.

Medicinal Product Interactions – Ritonavir with Protease Inhibitors

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of ritonavir (mg)	Medicinal Product Assessed	AUC	C_{min}
Amprenavir	600 q12h	100 q12h	Amprenavir[2]	↑ 64%	↑ 5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. Ritonavir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations. For further information, physicians should refer to the Agenerase Summary of Product Characteristics.				
Atazanavir	300 q24h	100 q24h	Atazanavir	↑ 86%	↑ 11 fold
			Atazanavir[1]	↑ 2 fold	↑ 3-7 fold

	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the Summary of Product Characteristics for atazanavir products.				
Darunavir	600, single	100 q12h	Darunavir	↑ 14 fold	
	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. Ritonavir doses higher than 100 mg twice daily have not been studied with darunavir. For further information, refer to the Summary of Product Characteristics for Prezista.				
Fosamprenavir	700 q12h	100 q12h	Amprenavir	↑ 2.4 fold	↑ 11 fold
	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. Clinical trials confirmed the safety and efficacy of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily. Ritonavir doses higher than 100 mg twice daily have not been studied with fosamprenavir. For further information, physicians should refer to the Telzir Summary of Product Characteristics.				
Indinavir	800 q12h	100 q12h	Indinavir[3]	↑ 178%	ND
			Ritonavir	↑ 72%	ND
	400 q12h	400 q12h	Indinavir[3]	↔	↑ 4 fold
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of indinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily. In cases of co-administration of ritonavir (100 mg twice daily) and indinavir (800 mg twice daily) caution is warranted as the risk of nephrolithiasis may be increased.				
Nelfinavir	1250 q12h	100 q12h	Nelfinavir	↑ 20to39%	ND
	750, single	500 q12h	Nelfinavir	↑ 152%	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily.				
Saquinavir	1000 q12h	100 q12h	Saquinavir[4]	↑ 15-fold	↑ 5-fold
			Ritonavir	↔	↔
	400 q12h	400 q12h	Saquinavir[4]	↑ 17-fold	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir100 mg twice daily with saquinavir 1000 mg twice daily provides saquinavir systemic exposure over 24 hours similar to or greater than those achieved with saquinavir 1200 mg three times daily without ritonavir. In a clinical study investigating the interaction of rifampicin 600 mg once daily and saquinavir 1000 mg with ritonavir 100 mg twice daily in healthy volunteers, severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration was noted. Due to the risk of severe hepatoxicity, saquinavir/ritonavir should not be given together with rifampicin. For further information, physicians should refer to the Invirase or Fortovase Summary of Product Characteristics.				
Tipranavir	500 q12h	200 q12h	Tipranavir	↑ 11 fold	↑ 29 fold
			Ritonavir	↓ 40%	ND
	Ritonavir increases the serum levels of tipranavir as a result of CYP3A inhibition. Tipranavir must be given with low dose ritonavir to ensure its therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used with tipranavir as they might alter the efficacy of the combination. For further information, physicians should refer to the Aptivus Summary of Product Characteristics.				

ND: Not determined.

1. Based on cross-study comparison to 400 mg atazanavir once daily alone.

2. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.
3. Based on cross-study comparison to 800 mg indinavir three times daily alone.
4. Based on cross-stud y comparison to 600 mg saquinavir three times daily alone.

Medicinal Product Interactions – Ritonavir with Antiretroviral Agents Other Than Protease Inhibitors

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of ritonavir (mg)	Medicinal Product Assessed	AUC	C_{min}
Didanosine	200 q12h	600 q12h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on an empty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Delavirdine	400 q8h	600 q12h	Delavirdine[1]	↔	↔
			Ritonavir	↑ 50%	↑ 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, dose reduction of ritonavir may be considered.				
Efavirenz	600 q24h	500 q12h	Efavirenz	↑ 21%	
			Ritonavir	↑ 17%	
	A higher frequency of adverse reactions (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Maraviroc	100 q12h	100 q12h	Maraviroc	↑ 161%	↑ 28%
	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for Celsentri.				
Nevirapine	200 q12h	600 q12h	Nevirapine	↔	↔
			Ritonavir	↔	↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either nevirapine or ritonavir.				
Zidovudine	200 q8h	300 q6h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.				

ND: Not determined
1. Based on parallel group comparison.

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
Alpha$_1$-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, piroxicam, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine, piroxicam, and propoxyphene and is therefore **contraindicated** (see section 4.3).			
Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is concomitantly administered with ritonavir.			
Methadone[1]	5, single dose	500 q12h,	↓ 36%	↓ 38%
	Increased methadone dose may be necessary when concomitantly administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.			
Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Antiarrthymics				
Amiodarone, bepridil, encainide, flecanide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecanide, propafenone, and quinidine and is therefore **contraindicated** (see section 4.3).			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND

	0.4 single oral dose	200 q12h, 13 days	↑ 22%	↔

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antriretroviral agent or as a pharmacokinetic enhancer. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops (see section 4.4).			
Antiasthmatic				
Theophylline[1]	3 mg/kg q8h	500 q12h	↓ 43%	↓ 32%
	An increased dose of theophyline may be required when co-administered with ritonavir, due to induction of CYP1A2.			
Anticancer agents				
Vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.			
Anticoagulant				
Warfarin	5, single dose	400 q12h		
S-Warfarin			↑ 9%	↓ 9%
R-Warfarin			↓ 33%	↔
	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S- warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Anticonvulsants				
Carbamazepine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of carbamazepine. Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with ritonavir.			
Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of desipramine, imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Desipramine	100, single oral dose	500 q12h	↑ 145%	↑ 22%
	The AUC and Cmax of the 2-hydroxy metabolite were decreased 15 and 67%, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir dosed as an antiretroviral agent.			
Trazodone	50, single dose	200 q12h	↑ 2.4-fold	↑ 34%
	An increase in the incidence in trazodone-related adverse reactions was noted when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If trazodone is co-administered with ritonavir, the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore **contraindicated** (see section 4.3).			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with ritonavir.			
Anti-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated** (see section 4.3).			
Rifabutin[1]	150 daily	500 q12h,	↑ 4-fold	↑ 2.5-fold
25-*O*-desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
	Due to the large increase in rifabutin AUC, the concomitant use of rifabutin with ritonavir dosed as an antiretroviral agent is **contraindicated** (see section 4.3). The reduction of the rifabutin dose to 150 mg 3 times per week may be indicated for select PIs when co-administered with ritonavir as a pharmacokinetic enhancer. The Summary of Product Characteristics of the co-administered protease inhibitor should be consulted for specific recommendations. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV-infected patients.			
Rifampicin	Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administered with rifampicin, the additional inducing effect of rifampicin (next to that of ritonavir itself) is small and may have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The effect of ritonavir on rifampicin is not known.			
Voriconazole	200 q12h	400 q12h	↓ 82%	↓ 66%
	200 q12h	100 q12h	↓ 39%	↓ 24%
	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole is **contraindicated** due to reduction in voriconazole concentrations (see section 4.3). Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.			
Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.			
Clarithromycin	500 q12h	200 q8h	↑ 77%	↑ 31%
14-OH clarithromycin metabolite			↓ 100%	↓ 99%
	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin and itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is used concomitantly administered with ritonavir.			
Ketoconazole	200 daily	500 q12h	↑ 3.4-fold	↑ 55%

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Sulfamethoxazole/Trimethoprim[2]	800/160, single dose	500 q12h	↓ 20% / ↑ 20%	↔
	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.			
Antipsychotics/Neuroleptics				
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore **contraindicated** (see section 4.3).			
Haloperidol, risperidone, thioridazine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.3).			
β2-agonist (long acting)				
Salmetarol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmetarol is expected. Therefore, concomitant use is not recommended.			
Calcium channel antagonists				
Amlodipine, diltiazem, nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Ergot Derivatives				
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore **contraindicated** (see section 4.3).			
Endothelin antagonists				
Bosentan	Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentr ations (C_{max}) and area under the curve (AUC).			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
HMG Co-A Reductase Inhibitors				
Atorvastatin, fluvastatin, lovastatin, pravstatin, rosuvastatin, simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is **contraindicated** (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.			
Hormonal contraceptive				
Ethinyl estradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32% Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives (see section 4.4).
Immunosupressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Phosphodiesterase inhibitors				
Sildenafil	100, single dose	500 q12h	↑ 11-fold	↑ 4-fold Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours (see also section 4.4). Concomitant use of sildenafil with ritonavir is **contraindicated** in pulmonary arterial hypertension patients (see section 4.3).
Tadalafil	20, single dose	200 q12h	↑ 124%	↔

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
	The concomitant use of tadalafil with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions (see section 4.4). When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC or prescribing information			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
	The concomitant use of vardenafil and ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse reactions (see section 4.4).			
Sedatives/hynoptics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			
Triazolam	0.125,single dose	200, 4 doses	↑ > 20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore **contraindicated** (see section 4.3).			
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
	The use of pethidine and ritonavir is **contraindicated** due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (eg, seizures), see section 4.3.			
Alprazolam	1, single dose	200 q12h, 2 days	↑2.5 fold	↔

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
		500 q12h, 10 days	↓ 12%	↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150	100 q12h	↓ 22%	↓ 21%
	150	600 q12h	↓ 66%	↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.			
Steroids				
Fluticasone propionate aqueous nasal spray	200 µg qd	100 q12h	↑ ~350-fold	↑ ~ 25-fold
	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86% in the above study) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A eg, budesonide. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (eg, beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of ritonavir (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
	longer period.			
Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.			
Prednisolone	20	200 q12h	↑ 28%	↑ 9%
	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.			

ND: Not determined
1. Based on a parallel group omparison
2. Sulfamethoxazole was co-administered with trimethoprim.

Cardiac and neurologic events have been reported when ritonavir has been co-administered with disopyramide, mexiletine or nefazadone. The possibility of medicinal product interaction cannot be excluded.

In addition to the interactions listed above, as ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medicinal products should be considered.

Proton pump inhibitors and H_2-receptor antagonists: proton pump inhibitors and H_2-receptor antagonists (e.g., omeprazole or ranitidine) may reduce concentrations for co-administered protease inhibitors. For specific information regarding the impact of co-administration of acid reducing agents, refer to the SmPC of the co-administered protease inhibitor. Based on interaction studies with the ritonavir boosted protease inhibitors (lopinavir/ritonavir, atazanavir), concurrent administration of omeprazole or ranitidine does not significantly modify ritonavir efficacy as a pharmacokinetic enhancer despite a slight change of exposure (about 6 - 18%).

4.6 Pregnancy and lactation

A limited number (> 800) of pregnant women were exposed to ritonavir during pregnancy; a very limited number (< 300) were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other PIs. These limited data 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 (see 5.3). The use of ritonavir may be considered in pregnancy only when the benefits outweigh the risk to the foetus.

Ritonavir adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during treatment.

Breast-Feeding

Current recommendations on HIV and breastfeeding (e.g., those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

It is not known whether this medicine is excreted in human milk. Milk excretion has not been

measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving or using machinery.

4.8 Undesirable effects

Ritonavir dosed as a pharmacokinetic enhancer

Adverse reactions associated with the use of ritonavir as a pharmacokinetic enhancer are dependent on the specific co-administered PI. For information on adverse reactions refer to the SmPC of the specific co-administered PI.

Ritonavir dosed as an antiretroviral agent

In the original clinical studies (Phase II/III), adverse reactions with possible, probable or unknown relationship to ritonavir were reported in ≥ 2% of 1033 patients.

The following adverse reactions of moderate to severe intensity with possible or probable relationship to ritonavir have been reported. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1000 to < 1/100); rare (> 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Events noted as having frequency not known were identified via post-marketing surveillance.

Undesirable effects in clinical studies and post-marketing in adult patients		
Blood and lymphatic system disorders	Common	Decreased WBC, decreased haemoglobin, decreased neutrophils, increased eosinophils
	Uncommon	Increased WBC, increased neutrophils and increased prothrombin time
	Not known	Thrombocytopenia
Immune system disorders	Common	Allergic reactions including urticaria, mild skin eruptions, bronchospasm and angioedema
	Rare	Anaphylaxis
Metabolic and nutritional disorders	Uncommon	Dehydration, diabetes mellitus
	Rare	Hyperglycaemia

	Not known	Hypertriglyceridaemia, hypercholesterolaemia, hyperuricaemia
Nervous system disorders	Very common	Taste perversion, circumoral and peripheral paresthesia, headache
	Common	Dizziness, paraesthesia, hyperaesthesia, somnolence, insomnia, anxiety
	Not known	Seizure, syncope
Vascular disorders	Common	Vasodilation
	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Pharyngitis, cough increased
Gastrointestinal disorders	Very common	Abdominal pain, nausea, diarrhoea, vomiting
	Common	Dyspepsia, anorexia, local throat irritation, flatulence, dry mouth, eructation, mouth ulcer
Hepatobiliary disorders	Uncommon	Hepatitis and jaundice
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, sweating, lipodystrophy
		Stevens Johnson syndrome
		Toxic epidermal necrolysis (TEN)
Musculosketal and connective tissue disorders	Common	Increased CPK, myalgia
	Uncommon	Myositis, rhabdomyolysis
Renal and urinary disorders	Not known	Acute renal failure
Reproductive system and breast disorders	Not known	Menorrhagia
General disorders and administration site conditions	Very common	Asthenia
	Common	Fever, pain weight loss
Investigations	Common	Increased GGT, increased CPK, increased triglycerides, increased SGPT, increased SGOT, increased amylase, increased uric acid, decreased potassium, decreased free and total thyroxin
	Uncommon	Increased glucose, decreased total calcium, increased magnesium, increased bilirubin, increased alkaline phosphatase

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

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

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

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 risk of elevated triglycerides and pancreatitis (see section 4.4).

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

4.9 Overdose

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paraesthesia, which resolved after the dose was decreased. A case of renal failure with eosinophilia has been reported.

The signs of toxicity observed in animals (mice and rats) included decreased activity, ataxia, dyspnoea and tremors.

There is no specific antidote for overdose with ritonavir. Treatment of overdose with ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Due to the solubility characteristics and possibility of transintestinal elimination, it is proposed that management of overdose could entail gastric lavage and administration of activated charcoal. Since ritonavir 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors ATC code: J05AE03

Ritonavir dosed as a pharmacokinetic enhancer

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor. For additional information on the effect of ritonavir on

co-administered protease inhibitor metabolism, see Section 4.5 and refer to the Summary of Product Characteristics of the particular co-administered PIs.

Ritonavir dosed as an antiretroviral agent

Ritonavir is an orally active 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 which 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 littleinhibitory activity against human aspartyl proteases.

Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. However, due to ritonavir's metabolic inhibitory properties its use as a pharmacokinetic enhancer of other protease inhibitors is the prevalent use of ritonavir in clinical practice (see section 4.2).

Effects on the Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) difference in QTcF from placebo was 5.5 (7.6) for 400 mg twice daily ritonavir. The Day 3 ritonavir exposure was approximately 1.5 fold higher thanthat observed with the 600 mg twice daily dose at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevantthreshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving ritonavir in the same study on Day 3. The mean changes from baseline in PR interval ranged from 11.0 to 24.0 msec in the 12-hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed (see section 4.4).

Resistance

Ritonavir-resistant isolates of HIV-1 have been selected *in vitro* and isolated from patients treated with therapeutic doses of ritonavir.

Reduction in the antiretroviral activity of ritonavir is primarily associated with the protease mutations V82A/F/T/S and I84V. Accumulation of other mutations in the protease gene (including at positions 20, 33, 36, 46, 54, 71, and 90) can also contribute to ritonavir resistance. In general, as mutations associated with ritonavir resistance accumulate, susceptibility to select other PIs may decrease due to cross-resistance. The Summary of Product Characteristics of other protease inhibitors or officialcontinuous updates should be consulted for specific information regarding protease mutations associated with reduced response to these agents.

Clinical pharmacodynamic data

The effects of ritonavir (alone or combined with other antiretroviral agents) on biological markers of disease activity such as CD4 cell count and viral RNA were evaluated in several studies involving HIV-1 infected patients. The following studies are the most important.

Adult Use

A controlled study completed in 1996 with ritonavir as add-on therapy in HIV-1 infected patientsextensively pre-treated with nucleoside analogues and baseline CD4 cell counts ≤ 100 cells/µl showed a reduction in mortality and AIDS defining events. The mean average change from baseline over 16 weeks for HIV RNA levels was -0.79 $\log_{10}$ (maximum mean decrease: 1.29 $\log_{10}$) in the ritonavir group versus -0.01 $\log_{10}$ in the control group. The most frequently used nucleosides in this study were zidovudine, stavudine, didanosine and zalcitabine.

In a study completed in 1996 recruiting less advanced HIV-1 infected patients (CD4 200-500 cells/µl) without previous antiretroviral therapy, ritonavir in combination with zidovudine or alone reduced viral load in plasma and increased CD4 count. The mean average change from baseline over 48 weeks for HIV RNA levels was -0.88 $\log_{10}$ in the ritonavir group versus -0.66 $\log_{10}$ in the ritonavir + zidovudine group versus -0.42 $\log_{10}$ in the zidovudine group.

The continuation of ritonavir therapy should be evaluated by viral load because of the possibility of the emergence of resistance as described under section 4.1 Therapeutic indications.

Paediatric Use

In an open label trial completed in 1998 in HIV infected, clinically stable children there was a significant difference ($p = 0.03$) in the detectable RNA levels in favour of a triple regimen (ritonavir, zidovudine and lamivudine) following 48 weeks treatment.

In a study completed in 2003, 50 HIV-1 infected, protease inhibitor and lamivudine naïve children age 4 weeks to 2 years received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with zidovudine 160 mg/m^2 every 8 hours and lamivudine 4 mg/kg every 12 hours. In intent to treatanalyses, 72% and 36% of patients achieved reduction in plasma HIV-1 RNA of ≤ 400 copies/ml at Week 16 and 104, respectively. Response was similar in both dosing regimens and across patient age.

In a study completed in 2000, 76 HIV-1 infected children aged 6 months to 12 years who were protease inhibitor naive and naive to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. In intent to treat analyses, 50% and 57% of patients in the 350 and 450 mg/m2 dose groups, respectively achieved reduction in plasma HIV-1 RNA to ≤ 400 copies/ml at Week 48.

5.2 Pharmacokinetic properties

The absorption characteristics of HA467 have been determined after administration of one (1) ritonavir 100mg tablet in healthy volunteers in the fed state, as follows:

Pharmacokinetic variable	**Mean value* ±standard deviation (ritonavir)**
Maximum concentration (C_{max})	859 ± 382 (787) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	7367 ± 3614 ng·h/mL
Time to attain maximum concentration (T_{max})	4.50 (2.00 – 7.00) h

*arithmetic mean

Absorption:

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined

Effects of food on oral absorption:

Food slightly decreases the bioavailability of the ritonavir. Administration of a single 100 mg dose of ritonavir with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and C_{max}.

Distribution:

The apparent volume of distribution (V_B/F) of ritonavir is approximately 20 - 40 L after a single600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 -

99% and is constant over the concentration range of 1.0 – 100 µg /ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.

Tissue distribution studies with ^{14}C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios ofapproximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Metabolism:
Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Animal studies as well as *in vitro* experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four 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 parent compound. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir (see section 4.5).

Elimination:
Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies, renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

Special Populations: No clinically significant differences in AUC or C_{max} were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass. Ritonavir plasma exposures in patients 50 – 70 years of age when dosed 100 mg in combination with lopinavir or at higher doses in the absence of other protease inhibitors is similar to that observed in younger adults.

Patients with impaired liver function: After multiple dosing of ritonavir to healthy volunteers (500 mg twice daily) and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B,
400 mg twice daily) exposure to ritonavir after dose normalisation was not significantly different between the two groups.

Patients with impaired renal function: Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

Paediatric patients: Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children above 2 years of age receiving doses ranging from 250 mg/m^2 twice daily to 400 mg/m^2 twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in paediatric patients
were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2) was approximately 1.5 to 1.7 times faster in paediatric patients above 2 years of age than in adult subjects.

Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in

adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2) declined with age with median values of 9.0 L/h/m^2 in children less than 3 months of age, 7.8 L/h/m^2 in children between 3 and 6 months of age and 4.4 L/h/m^2 in children between 6 and 24 months of age.

5.3 Preclinical safety data

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea werennoted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Developmental toxicity observed in rats (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

Ritonavir was not found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Long term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species but are regarded as of no relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Colloidal silicon dioxide, copovidone, sodium chloride, sodium stearyl fumarate, sorbitan monolaurate.

Film coating: Colloidal anhydrous silica, hypromellose, hydroxypropyl cellulose, iron oxide yellow, polyethylene glycol, polysorbate 80, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in original container

6.5 Nature and contents of the packaging

- White, opaque HDPE bottle with white, opaque cap with inbuilt desiccant. Pack size: 30 tablets and 120 tablets.
- White HDPE bottle with white opaque polypropylene screw closure with aluminium induction sealing liner and 2g silica gel desiccant canister. Pack size: 120 tablets.

- White HDPE bottle with white opaque polypropylene screw closure with aluminium induction sealing liner and 1g silica gel desiccant canister. Pack size: 30 tablets.
- Alu-Alu cold form blister of 10 tablets.1 such blister packed in a carton box.

6.6 Special precautions for disposal
No special requirements.

7. SUPPLIER
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14 December 2010

10. DATE OF REVISION OF THE TEXT
May 2023

11. References
General
European SmPC for Norvir (ritonavir) available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000127/WC500028728.pdf

Antiretroviral Therapy for HIV Infection in Adults and Adolescents , Recommendations for a Public Health Approach, 2010 Revision, World Health Organization, Geneva, available at:
http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf

Ritonavir-boosted protease inhibitors in HIV therapy
Hull MD, Montaner, JS Ann Med 2011 43;5:375-88

References relevant to sections of the SmPC
4.6 Pregnancy and lactation
Breastfeeding
WHO: Guidelines on HIV and infant feeding 2010:
http://www.who.int/child_adolescent_health/documents/9789241599535/en/index.html

5. Drug interactions
The University of Liverpool HIV drug interactions database,
available at: http://www.hiv-druginteractions.org/

5.1 Pharmacodynamic properties
Virology
The Stanford HIV drug resistance database, available at: http://hivdb.stanford.edu/