

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Norvir 80 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 80 mg of ritonavir.

Excipients with known effect:

Alcohol (43,2 % v/v)

Propylene glycol (26.0% v/v)

Polyoxyl 35 Castor Oil

Sunset Yellow (E110)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

The solution is a practically clear, orange solution for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ritonavir is 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).

4.2 Posology and method of administration

Ritonavir should be administered by physicians who are experienced in the treatment of HIV infection.

Norvir solution is administered orally and should preferably be ingested with food.

Ritonavir dosed as a pharmacokinetic enhancer

When ritonavir is 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/200mg.

Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART experienced patients.

Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART-naïve patients.

Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients).

Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients.

Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients.

Paediatric use: Ritonavir is 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. Norvir is 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, ritonavir 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 (SPC) 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 SPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

Ritonavir dosed as an antiretroviral agent

Adult use: The recommended dosage of Norvir solution is 600 mg (7.5 ml) twice daily by mouth.

Gradually increasing the dose of ritonavir when initiating therapy may help to improve tolerance. Treatment should be initiated at 300 mg (3.75 ml) twice daily for a period of three days and increased by 100 mg (1.25 ml) twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days.

Paediatric use (2 years of age and above): the recommended dosage of Norvir solution in children is 350 mg/m² by mouth twice daily and should not exceed 600 mg twice daily. Norvir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. The dose should be administered using a calibrated dosing syringe.

Paediatric Dosage Guidelines

Body Surface area* (m ²)	Twice daily dose 250 mg/m ²	Twice daily dose 300 mg/m ²	Twice daily dose 350 mg/m ²
0.25	0.8 ml (62.5 mg)	0.9 ml (75 mg)	1.1 ml (87.5 mg)
0.50	1.6 ml (125 mg)	1.9 ml (150 mg)	2.2 ml (175 mg)
1.00	3.1 ml (250 mg)	3.8 ml (300 mg)	4.4 ml (350 mg)
1.25	3.9 ml (312.5 mg)	4.7 ml (375 mg)	5.5 ml (437.5 mg)
1.50	4.7 ml (375 mg)	5.6 ml (450 mg)	6.6 ml (525 mg)

* Body surface area can be calculated with the following equation

$$\text{BSA (m}^2\text{)} = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)}) / 3600}$$

Doses for intermediate body surface areas not included in the above table can be calculated using the following equations:

To calculate the volume to be administered (in ml) the body surface area should be multiplied by a factor of: 3.1 for a dose of 250 mg/m²; 3.8 for one of 300 mg/m²; and by 4.4 for 350 mg/m².

Ritonavir oral solution also contains propylene glycol (26.0% v/v). Total amounts of alcohol and propylene glycol from all medicines, including ritonavir oral solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients (see section 4.4)

Renal impairment: Currently, there are no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearance of ritonavir is negligible; therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment: Ritonavir is principally metabolised and eliminated by the liver. Pharmacokinetic data indicate that no dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2). Ritonavir should not be given to patients with severe hepatic impairment (see section 4.3).

Older people: Pharmacokinetic data indicated that no dose adjustment is necessary for older patients (see section 5.2).

The bitter taste of Norvir solution may be lessened if mixed with chocolate milk.

4.3 Contraindications

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

When ritonavir is used as a pharmacokinetic enhancer of other PIs, consult the Summary of Product Characteristics of the co-administered protease inhibitor for contraindications.

Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent 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 medicinal product and risk of clinically significant adverse effects.

The enzyme-modulating effect of ritonavir may be dose dependent. For some products, contraindications may be more relevant when ritonavir is used as an antiretroviral agent than when ritonavir is used as a pharmacokinetic enhancer (e.g. rifabutin and voriconazole):

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased or decreased		
α_1 -Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 4.5).

Analgesics	Pethidine, piroxicam, propoxyphne	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.
Antiarrhythmics	Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse reactions 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 due to an increase of rifabutin serum concentrations and risk of adverse events 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.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
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 Inhibitor	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).

	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 section 4.4 and section 4.5 for coadministration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
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 parenterally administered midazolam, see section 4.5).
Ritonavir medicinal product level decreased		
Herbal Preparation	St. John's wort	Herbal preparations containing St John's wort (<i>Hypericum perforatum</i>) 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

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving ritonavir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 Product Characteristics for the particular PI must be consulted.

Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer

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 haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should 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 Norvir 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 asymptomatic 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 jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

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, 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 (SPC) of the co-administered protease inhibitor. See also section 4.2.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8).

Ritonavir oral solution contains castor oil polyoxyl which may cause stomach upset and diarrhoea. Ritonavir oral solution also contains the azo-colouring agent sunset yellow (E110) which may cause allergic reactions.

Ritonavir oral solution contains alcohol (43 % v/v), ie up to 2572.5 mg per maximum dose of 600 mg, equivalent to 81 ml beer (4%), 23 ml wine (14%) per dose. Each 100 mg dose contains up to 428.8 mg alcohol and each 200 mg dose contains 857.5 mg alcohol. Therefore concomitant administration of Norvir with disulfiram or medicines with disulfiram-like reactions (e.g. metronidazole) should be avoided. Also to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

Particular risk of toxicity in relation to the amount of alcohol and propylene glycol contained in the oral solution of Norvir.

Healthcare professionals should be aware that Norvir oral solution is highly concentrated and contains the excipients alcohol (43.2% v/v) and propylene glycol (26.0% v/v). 5 ml of Norvir solution (for antiretroviral purposes) contains 1.7 g of alcohol and 1.3 g propylene glycol. 1 ml of Norvir solution (for pharmacokinetic enhancer purposes) contains 344.0 mg of alcohol and 265.7 mg propylene glycol.

Special attention should be given to accurate calculation of the dose of Norvir, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children.

Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients. Infants should be monitored closely for toxicity related to Norvir oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, central nervous system (CNS) depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Postmarketing life-threatening cases of cardiac toxicity (including complete atrioventricular (AV) block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving ritonavir oral solution (see sections 4.3 and 4.9).

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. Norvir should be used with caution in such patients (see section 5.1).

Interactions with other medicinal products

Ritonavir dosed as an antiretroviral agent

The following Warnings and Precautions should be considered when ritonavir is used as an antiretroviral agent. When ritonavir is used as a pharmacokinetic enhancer at the 100 mg and 200 mg level it cannot be assumed that the following warnings and precautions will also apply. When ritonavir is used as a pharmacokinetic enhancer, full details on the warnings and precautions relevant to that particular PI must be considered, therefore the Summary of Product Characteristics, section 4.4, for the particular PI must be consulted to determine if the information below is applicable.

PDE5 inhibitors: Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse reactions such as hypotension and prolonged erection (see section 4.5). Concomitant use of avanafil or vardenafil with ritonavir is contraindicated. Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see section 4.3).

HMG-CoA reductase inhibitors: The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A. 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 doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent of CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Digoxin: Particular caution should be used when prescribing ritonavir in patients taking digoxin since co-administration of ritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels may lessen over time (see section 4.5).

In patients who are already taking digoxin when ritonavir is introduced, the digoxin dose should be reduced to one-half of the patients' normal dose and patient need to be followed more closely than usual for several weeks after initiating co-administration of ritonavir and digoxin.

In patients who are already taking ritonavir when digoxin is introduced, digoxin should be introduced more gradually than usual. Digoxin levels should be monitored more intensively than usual during this period, with dose adjustments made, as necessary, based on clinical, electrocardiographic and digoxin level findings.

Ethinyl estradiol: Barrier or other non-hormonal methods of contraception should be considered when administering ritonavir at therapeutic or low doses as ritonavir is likely to reduce the effect and change the uterine bleeding profile when co-administered with estradiol-containing contraceptives.

Glucocorticoids: Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Trazodone: Particular caution should be used when prescribing ritonavir in patients using trazodone. Trazodone is a CYP3A4 substrate and co-administration of ritonavir is expected to increase trazodone levels. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed in single dose interaction studies in healthy volunteers (see section 4.5)

Rivaroxaban: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding (see section 4.5).

Bedaquiline: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline Summary of Product Characteristics).

Ritonavir dosed as a pharmacokinetic enhancer

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

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

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 Norvir 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 decrease 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 (e.g. delavirdine, efavirenz, phenytoin and rifampicin). These interactions are noted in the medicinal product interaction tables below.

Medicinal product 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 NORVIR (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. Norvir 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 Atazanavir ¹	↑ 86% ↑ 2 fold	↑ 11 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 Reyataz Summary of Product Characteristics.					
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
Indinavir	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. Ritonavir 100 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 hepatotoxicity, 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 NORVIR (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 (e.g., 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.					
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels					
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 NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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Alpha₁-Adrenoreceptor Antagonist

Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore contraindicated (see section 4.3).			
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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).			
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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 SPC 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).			
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Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 (including respiratory depression) 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.			

Antiarrhythmics

Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine and is therefore contraindicated (see section 4.3).			
Digoxin	0.5 single IV dose 0.4 single oral dose	300 q12h, 3 days 200 q12h, 13 days	↑ 86% ↑ 22%	ND ↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antiretroviral 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 theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.			

Anticancer agents

Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.			
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Anticoagulant

Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12h	↑ 9% ↓ 33%	↓ 9% ↔
<p>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.</p>				
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.			
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 C _{max} 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.				
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 antiretroviral 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 loratadine 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- <i>O</i> -desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	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 200 q12h	400 q12h 100 q12h	↓ 82% ↓ 39%	↓ 66% ↓ 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.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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.	
Bedaquiline			No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline Summary of Product Characteristics).	
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 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).			
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Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Haloperidol, risperidone, thioridazine				
Quetiapine				
β2-agonist (long acting)				
Salmeterol				
Calcium channel antagonists				
Amlodipine, diltiazem, nifedipine				
Endothelin antagonists				
Bosentan				
Ergot Derivatives				
Dihydroergotamine, ergonovine, ergotamine, methylergonovine				
GI motility agent				
Cisapride				
HCV Protease Inhibitor				
Simeprevir	200 qd	100 q12h	↑ 7.2-fold	↑ 4.7-fold

Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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HMG Co-A Reductase Inhibitors

Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, 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%
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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).

Immunosuppressants

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 (PDE5) inhibitors

Avanafil

50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
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Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).

Sildenafil

100, single dose	500 q12h	↑ 11-fold	↑ 4-fold
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Concomitant use of sildenafil for the treatment of erectile dysfunction, with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be used 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).

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
<p>The concomitant use of tadalafil for the treatment of erectile dysfunction 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).</p> <p>When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC or prescribing information</p>				
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
<p>Concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).</p>				

Sedatives/hypnotics

Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	<p>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 Norvir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of Norvir 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, Norvir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Norvir 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 Norvir 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.</p>			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
<p>Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3).</p>				
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
<p>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 (e.g., seizures), see section 4.3.</p>				
Alprazolam	1, single dose	200 q12h, 2 days	↑ 2.5 fold	↔
			500 q12h, 10 days	↓ 12%
				↓ 16%

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
	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 e.g., 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 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 comparison 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.

Ritonavir dosed as a pharmacokinetic enhancer

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

Proton pump inhibitors and H₂-receptor antagonists: proton pump inhibitors and H₂-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 Fertility, 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 section 5.3). The use of Norvir 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.

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. HIV infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV.

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.

Norvir oral solution contains alcohol (43%).

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 SPC of the specific co-administered PI.

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia) and fatigue/asthenia.

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 a frequency not known were identified via post-marketing surveillance

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Decreased WBC, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
Immune system disorders	Common	Hypersensitivity, including urticaria and face oedema.
	Rare	Anaphylaxis

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Metabolic and nutritional disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very Common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia
	Common	Anorexia, , flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia and back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g. oliguria, elevated creatinine)
	Uncommon	Acute renal failure

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common	Increased amylase, decreased free and total thyroxin
	Uncommon	Increased glucose, increased magnesium, 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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in [Appendix V](#)**.

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.

Overdoses with other ritonavir oral solutions have been reported (including fatal outcome). The following events have been reported in association with unintended overdoses in preterm neonates: complete atrioventricular block, cardiomyopathy, lactic acidosis, and acute renal failure.

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. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with ritonavir oral solution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antiviral 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 little inhibitory 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 than that 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 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. 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 official continuous 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 patients extensively 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.

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 treat analyses, 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 naïve and naïve 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/m^2 dose groups, respectively, achieved reduction in plasma HIV-1 RNA to ≤ 400 copies/ml at Week 48.

5.2 Pharmacokinetic properties

Absorption:

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV-infected adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. The time to maximum concentration (T_{max}) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0.1 l/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosing schemes of ritonavir alone are shown in the table below.

	Ritonavir Dosing Regimen				
	100 mg once daily	100 mg twice daily ¹	200 mg once daily	200 mg twice daily	600 mg twice daily
C_{max} (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3	11.2 ± 3.6
C_{trough} (µg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2	3.7 ± 2.6
AUC _{12 or 24} (µg•h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48	77.5 ± 31.5
$t_{1/2}$ (h)	~5	~5	~4	~8	~3 to 5
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2	8.8 ± 3.2

¹ Values expressed as geometric means. Note: ritonavir was dosed after a meal for all listed regimens.

Effects of food on oral absorption:

Ingestion of ritonavir with food results in higher ritonavir exposure than ingestion in the fasted state.

Distribution:

The apparent volume of distribution (V_B/F) of ritonavir is approximately 20 - 40 l after a single 600 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 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 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/m² twice daily to 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m²) 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/m²) declined with age with median values of 9.0 L/h/m² in children less than 3 months of age, 7.8 L/h/m² in children between 3 and 6 months of age and 4.4 L/h/m² 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 proteinuria were noted 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 (embryo lethality, 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 (embryo lethality, 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

Norvir oral solution contains:

alcohol,
purified water,
polyoxyl 35 castor oil,
propylene glycol,
anhydrous citric acid,
saccharin sodium,
peppermint oil,
creamy caramel flavour,
sunset yellow E110.

6.2 Incompatibilities

Norvir should not be diluted with water.

6.3 Shelf life

6 months

6.4 Special precautions for storage

Store below 25°C and use within the expiry date shown on the bottle. Do not refrigerate or freeze.

Avoid exposure to excessive heat. Keep the bottle tightly closed.

6.5 Nature and contents of container

Norvir oral solution is supplied in amber coloured multiple-dose polyethylene terephthalate (PET) bottles in a 90 ml size.

Two pack sizes are available for Norvir oral solution:

- 1 bottle of 90 ml (90 ml) plus one 7.5 ml dosing syringe.
- Multipack containing 450 ml (5 bottles of 90 ml) oral solution plus five 7.5 ml dosing syringes.

The 7.5 ml dosing syringe has graduations from 0.8 ml to 7.5 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Shake well before each use. If, after shaking, particles or precipitate can be seen in the solution, the patient should take the next dose and see their doctor about a fresh supply.

The oral syringe should be cleaned immediately with hot water and dish soap after use. When cleaned immediately, drug residue is removed. The device **must** be dry prior to use.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/001
EU/1/96/016/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 1996
Date of latest renewal: 26 August 2006

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of powder for oral suspension contains 100 mg of ritonavir.

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

Beige/pale yellow to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ritonavir is 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).

4.2 Posology and method of administration

Ritonavir should be administered by physicians who are experienced in the treatment of HIV infection.

Posology

Ritonavir dosed as a pharmacokinetic enhancer

When ritonavir is 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.

Adults

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/200mg.

Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART experienced patients.

Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART-naïve patients.

Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients.

Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients.

Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients.

Children and adolescents

Ritonavir is 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.

Special populations

Renal impairment

As ritonavir is primarily metabolised by the liver, ritonavir 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 (SPC) 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 SPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

Ritonavir dosed as an antiretroviral agent

Adults

The recommended dose of Norvir powder for oral suspension is 600 mg (six sachets) twice daily by mouth and should be given with food.

Gradually increasing the dose of ritonavir when initiating therapy may help to improve tolerance. Treatment should be initiated at 300 mg (three sachets) twice daily for a period of three days and increased by 100 mg (one sachet) twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days.

Refer to Method of Administration section below and section 6.6 for details on preparing doses.

Children and adolescents (2 years of age and above)

The recommended dosage of Norvir powder for suspension in children is 350 mg/m² by mouth twice daily and should not exceed 600 mg twice daily. Norvir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily.

Paediatric dosage guidelines for Norvir powder for oral suspension (prepared as 100 mg/10 mL)*†

Body Surface Area (m²)	Twice Daily Dose 250 mg/m²	Twice Daily Dose 300 mg/m²	Twice Daily Dose 350 mg/m²
0.25	6.4 mL (62.5 mg)	7.6 mL (76 mg)	8.8 mL (88 mg)
0.50	12.6 mL (126 mg)	15.0 mL (150 mg)	17.6 mL (176 mg)
0.75	18.8 mL (188 mg)	22.6 mL (226 mg)	26.4 mL (262.5 mg)
1.00	25.0 mL (250 mg)	30.0 mL (300 mg)	35.0 mL (350 mg)
1.25	31.4 mL (312.5 mg)	37.6 mL (376 mg)	43.8 mL (438mg)
1.50	37.6 mL (376 mg)	45.0 mL (450 mg)	52.6 mL (526 mg)

*When mixed with 9.4 mL of liquid the concentration of the suspension is 10 mg/mL.

†In some instances, the volumes and/or doses have been adjusted to ensure the recommended final dose and dosing volume.

Body surface area can be calculated with the following equation: $BSA (m^2) = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)}) / 3600}$

To calculate the volume to be administered (in mL) for intermediate body surface areas not included in the above table, the body surface area should be multiplied by a factor of: 25 for a dose of 250 mg/m²; 30 for 300 mg/m²; and 35 for 350 mg/m².

Refer to Method of Administration section below and section 6.6 for details on preparing doses.

Special populations

Elderly

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

Renal impairment

Currently, there are no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearance of ritonavir is negligible; therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment

Ritonavir is principally metabolised and eliminated by the liver. Pharmacokinetic data indicate that no dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2). Ritonavir must not be given to patients with severe hepatic impairment (see section 4.3).

Paediatric population The safety and efficacy of Norvir in children aged below 2 years has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Norvir powder for oral suspension is administered orally, poured on soft food (apple sauce or vanilla pudding) or mixed with liquid (water, chocolate milk, or infant formula). For details on preparation and administration of the Norvir powder for oral suspension, see section 6.6. Any mixing outside the recommendations is the responsibility of the health care professional or the user.

Norvir powder for oral suspension should be taken with food. The bitter aftertaste of Norvir powder for oral suspension may be lessened if peanut butter, hazelnut chocolate spread, or black currant syrup are taken immediately after dose administration.

The prescribed dose of Norvir powder for oral suspension can be administered via a feeding tube after being mixed with water as detailed in section 6.6. Follow the instructions for the feeding tube to administer the medicine.

4.3 Contraindications

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

When ritonavir is used as a pharmacokinetic enhancer of other PIs, consult the Summary of Product Characteristics of the co-administered protease inhibitor for contraindications.

Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent 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 medicinal product and risk of clinically significant adverse effects.

The enzyme-modulating effect of ritonavir may be dose dependent. For some products, contraindications may be more relevant when ritonavir is used as an antiretroviral agent than when ritonavir is used as a pharmacokinetic enhancer (eg rifabutin and voriconazole):

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased or decreased		
α_1 -Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 4.5).
Analgesics	Pethidine, piroxicam, propoxyphne	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.
Antiarrhythmics	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 reactions 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 due to an increase of rifabutin serum concentrations and risk of adverse events 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, pimozone	Increased plasma concentrations of clozapine and pimozone. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.

	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
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 Inhibitor	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
PDE5 inhibitors	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
	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 section 4.4 and section 4.5 for coadministration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
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 parenterally administered midazolam, see section 4.5).
Ritonavir medicinal product level decreased		
Herbal Preparation	St. John's wort	Herbal preparations containing St John's wort (<i>Hypericum perforatum</i>) 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

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving ritonavir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 Product Characteristics for the particular PI must be consulted.

Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer

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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should 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 Norvir 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 asymptomatic 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.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Liver disease

Ritonavir should not be given to patients with decompensated liver disease (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, the decrease in the total body clearance is not expected in patients with renal impairment (see also section 4.2).

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8).

Medication error

Special attention should be given to the accurate calculation of the dose of Norvir, transcription of the medication order, dispensing information and dosing instructions to minimise the risk for medication errors and underdosing. This is especially important for infants and young children.

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 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. Norvir should be used with caution in such patients (see section 5.1).

Interactions with other medicinal products

Ritonavir dosed as an antiretroviral agent

The following warnings and precautions should be considered when ritonavir is used as an antiretroviral agent. When ritonavir is used as a pharmacokinetic enhancer at the 100 mg and 200 mg level it cannot be assumed that the following warnings and precautions will also apply. When ritonavir is used as a pharmacokinetic enhancer, full details on the warnings and precautions relevant to that particular PI must be considered, therefore the Summary of Product Characteristics, section 4.4, for the particular PI must be consulted to determine if the information below is applicable.

PDE5 inhibitors

Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse reactions such as hypotension and prolonged erection (see section 4.5). Concomitant use of avanafil or vardenafil with ritonavir is contraindicated (see section 4.3). Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see section 4.3).

HMG-CoA reductase inhibitors

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A. 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 doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent of CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Digoxin

Particular caution should be used when prescribing ritonavir in patients taking digoxin since co-administration of ritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels may lessen over time (see section 4.5).

In patients who are already taking digoxin when ritonavir is introduced, the digoxin dose should be reduced to one-half of the patients' normal dose and patient need to be followed more closely than usual for several weeks after initiating co-administration of ritonavir and digoxin.

In patients who are already taking ritonavir when digoxin is introduced, digoxin should be introduced more gradually than usual. Digoxin levels should be monitored more intensively than usual during this period, with dose adjustments made, as necessary, based on clinical, electrocardiographic and digoxin level findings.

Ethinyl estradiol

Barrier or other non-hormonal methods of contraception should be considered when administering ritonavir at therapeutic or low doses as ritonavir is likely to reduce the effect and change the uterine bleeding profile when co-administered with estradiol-containing contraceptives.

Glucocorticoids

Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Trazodone

Particular caution should be used when prescribing ritonavir in patients using trazodone. Trazodone is a CYP3A4 substrate and co-administration of ritonavir is expected to increase trazodone levels. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed in single dose interaction studies in healthy volunteers (see section 4.5)

Rivaroxaban

It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding (see section 4.5).

Bedaquiline

Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline Summary of Product Characteristics).

Ritonavir dosed as a pharmacokinetic enhancer

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

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

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 selected 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 (eg 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 decrease 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, St John's wort should be stopped 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 (e.g. delavirdine, efavirenz, phenytoin and rifampicin). These interactions are noted in the medicinal product interaction tables below.

Medicinal product 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 NORVIR (mg)	Medicinal Product Assessed	AUC	C_{min}
Amprenavir	600 q12h	100 q12h	Amprenavir ¹	↑ 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. Norvir 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 Summary of Product Characteristics for amprenavir.					
Atazanavir	300 q24h	100 q24h	Atazanavir Atazanavir ²	↑ 86% ↑ 2 fold	↑ 11 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.					
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 darunavir.					
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 Summary of Product Characteristics for fosamprenavir.					
Indinavir	800 q12h	100 q12h	Indinavir ³ Ritonavir	↑ 178% ↑ 72%	ND ND
	400 q12h	400 q12h	Indinavir ³ Ritonavir	↔ ↔	↑ 4 fold ↔
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. Ritonavir 100 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 hepatotoxicity, 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 Summary of Product Characteristics for tipranavir.					
ND: Not determined.					
1. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.					
2. Based on cross-study comparison to 400 mg atazanavir once daily alone.					
3. Based on cross-study comparison to 800 mg indinavir three times daily alone.					
4. Based on cross-study 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 NORVIR (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.					
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels					
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 NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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Alpha₁-Adrenoreceptor Antagonist

Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore contraindicated (see section 4.3).			
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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).			
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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 SPC 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).			
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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 (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.			
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Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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.			

Antiarrhythmics

Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine and is therefore contraindicated (see section 4.3).			
Digoxin	0.5 single IV dose 0.4 single oral dose	300 q12h, 3 days 200 q12h, 13 days	↑ 86% ↑ 22%	ND ↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antiretroviral 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 theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.			

Anticancer agents

Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.			
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Anticoagulant

Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12h	↑ 9% ↓ 33%	↓ 9% ↔
<p>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.</p>				
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.			
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 C _{max} 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.				
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 antiretroviral 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 loratadine 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- <i>O</i> -desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	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 200 q12h	400 q12h 100 q12h	↓ 82% ↓ 39%	↓ 66% ↓ 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.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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.			
Bedaquiline	No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline Summary of Product Characteristics).			
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 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).			
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Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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.				
Quetiapine				
Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Norvir and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see section 4.3).				
β2-agonist (long acting)				
Salmeterol				
Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol 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.				
Endothelin antagonists				
Bosentan				
Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentrations (C _{max}) and area under the curve (AUC)				
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).				
GI motility agent				
Cisapride				
Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride and is therefore contraindicated (see section 4.3).				
HCV Protease Inhibitor				
Simeprevir	200 qd	100 q12h	↑ 7.2-fold	↑ 4.7-fold
Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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HMG Co-A Reductase Inhibitors

Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, 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).

Immunosuppressants

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 (PDE5) inhibitors

Avanafil

50, single dose 600 q12h ↑ 13-fold ↑ 2.4-fold

Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).

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 used 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).

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
<p>The concomitant use of tadalafil for the treatment of erectile dysfunction 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).</p> <p>When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC or prescribing information</p>				
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
<p>Concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).</p>				

Sedatives/hypnotics

Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	<p>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).</p> <p>Midazolam is extensively metabolised by CYP3A4. Co-administration with Norvir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of Norvir 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, Norvir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Norvir 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 Norvir 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.</p>			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
<p>Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3).</p>				
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
<p>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.</p>				
Alprazolam	1, single dose	200 q12h, 2 days	↑ 2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
	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 longer period.				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 comparison
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.

Ritonavir dosed as a pharmacokinetic enhancer

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

Proton pump inhibitors and H₂-receptor antagonists

Proton pump inhibitors and H₂-receptor antagonists (eg 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 Fertility, pregnancy and lactation

Pregnancy

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 section 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.

Breastfeeding

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. HIV infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV.

Fertility

No human data on the effect of ritonavir on fertility are available. Animal studies do not indicate harmful effects of ritonavir on fertility (see section 5.3).

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. Dizziness is a known undesirable effect that should be taken into account when driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

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 SPC of the specific co-administered PI.

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhoea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paraesthesia and oral paraesthesia) and fatigue/asthenia.

Tabulated list of adverse reactions

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 a frequency not known were identified via post-marketing surveillance

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Immune system disorders	Common	Hypersensitivity, including urticaria and face oedema.
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very Common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia
	Common	Anorexia, , flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia and back pain

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (eg oliguria, elevated creatinine)
	Uncommon	Acute renal failure
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common	Increased amylase, decreased free and total thyroxine
	Uncommon	Increased glucose, increased magnesium, increased alkaline phosphatase

Description of selected adverse reactions

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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (see section 4.4).

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia. 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).

Paediatric populations

The safety profile of Norvir in children 2 years of age and older is similar to that seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Symptoms

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.

Management

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

Pharmaco-therapeutic group: antiviral 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 little inhibitory 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 than that 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 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. 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 official continuous 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 patients extensively pre-treated with nucleoside analogues and baseline CD4 cell counts ≤ 100 cells/ μ l 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/ μ l) 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.

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/m² every 12 hours co-administered with zidovudine 160 mg/m² every 8 hours and lamivudine 4 mg/kg every 12 hours. In intent to treat analyses, 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 naïve and naïve to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m² 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

Absorption

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability has not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV-infected adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. The time to maximum concentration (T_{max}) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0.1 l/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosing schemes of ritonavir alone are shown in the table below.

	Ritonavir Dosing Regimen				
	100 mg once daily	100 mg twice daily ¹	200 mg once daily	200 mg twice daily	600 mg twice daily
C _{max} (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3	11.2 ± 3.6
C _{trough} (µg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2	3.7 ± 2.6
AUC _{12 or 24} (µg•h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48	77.5 ± 31.5
t _{1/2} (h)	~5	~5	~4	~8	~3 to 5
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2	8.8 ± 3.2

¹ Values expressed as geometric means. Note: ritonavir was dosed after a meal for all listed regimens.

Ritonavir AUC and C_{max} after administration of a single 100 mg dose powder for oral suspension are bioequivalent to the 100 mg oral solution under fed conditions.

Effects of food on oral absorption

Administration of a single 100 mg dose of ritonavir powder for oral suspension with a moderate fat meal (617 kcal, 29% calories from fat) was associated with a mean decrease of 23 and 39% in ritonavir AUC_{inf} and C_{max} respectively, relative to fasting conditions. Administration with a high fat meal (917 kcal, 60% calories from fat) was associated with a mean decrease of 32 and 49% in ritonavir AUC_{inf} and C_{max} respectively, relative to fasting conditions.

Distribution

The apparent volume of distribution (V_B/F) of ritonavir is approximately 20 - 40 l after a single 600 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 of approximately 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/m² twice daily to 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m²) 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/m²) declined with age with median values of 9.0 L/h/m² in children less than 3 months of age, 7.8 L/h/m²

in children between 3 and 6 months of age and 4.4 L/h/m² 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 proteinuria were noted 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 (embryo lethality, 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 (embryo lethality, 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

Copovidone
Sorbitan laurate
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.
Following mixing with food or liquid as described in section 4.2: consume within 2 hours.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Polyethylene/aluminium/polyethylene terephthalate foil sachet. 30 sachets per carton. Packaged with a mixing cup and two 10 mL calibrated oral dosing syringes.

6.6 Special precautions for disposal and other handling

For details on preparation and administration of Norvir powder for oral suspension, refer the patient or care giver to the Package Leaflet, section 3.

Administering with food

- The entire contents of each sachet is to be poured over a small amount of soft food (e.g. apple sauce or vanilla pudding). All of the mixed soft food must be administered within 2 hours.

Administering with liquid

The entire contents of each sachet should be suspended in 9.4 mL of liquid (water, chocolate milk, or infant formula) giving a final concentration of 10 mg per mL. The patient/caregiver is to be instructed to follow the directions below:

- The oral dosing syringe and mixing cup should be dry prior to use.
- Draw up 9.4 mL of liquid using the provided oral dosing syringe, remove the bubbles, and transfer the liquid to the mixing cup. All measuring should be done in mL using the syringe.
- Pour the entire contents of 1 sachet (100 mg) into the mixing cup.
- Close the lid and shake hard for at least 90 seconds until all the lumps have dissolved.
- Let the liquid stand for 10 minutes in order for most of the bubbles to disappear.
- Use the provided oral dosing syringe to measure and administer the prescribed mL volume (see section 4.2). Be sure to remove the bubbles prior to dose administration.
- Once the powder is mixed, the prepared suspension should be used within 2 hours.
- Discard any mixture remaining in the mixing cup.
- The oral dosing syringe and mixing cup should be cleaned immediately with warm water and dish soap after use.
- If the syringe breaks or becomes hard to use, the syringe should be thrown away and the new one used.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 1996

Date of latest renewal: 26 August 2006

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg ritonavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, oval, debossed with [Abbott logo] and “NK”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ritonavir is 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).

4.2 Posology and method of administration

Ritonavir should be administered by physicians who are experienced in the treatment of HIV infection.

Ritonavir film-coated tablets are administered orally and should be ingested with food (see section 5.2).

Norvir film-coated tablets should be swallowed whole and not chewed, broken or crushed.

Ritonavir dosed as a pharmacokinetic enhancer

When ritonavir is 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 in ART experienced patients. Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in ART-naïve patients.

Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients.

Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment. (ART) experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. Refer to the darunavir SmPC for further information on once daily dosing in ART experienced patients.
 Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients.

Paediatric use: Ritonavir is 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. Norvir is 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, ritonavir 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 (SPC) 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 SPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

Ritonavir dosed as an antiretroviral agent

Adult use: The recommended dose of Norvir film-coated tablets is 600 mg (6 tablets) twice daily (total of 1200 mg per day) by mouth.

Gradually increasing the dose of ritonavir when initiating therapy may help to improve tolerance. Treatment should be initiated at 300 mg (3 tablets) twice daily for a period of three days and increased by 100 mg (1 tablet) twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days.

Paediatric use (2 years of age and above): the recommended dosage of Norvir in children is 350 mg/m² by mouth twice daily and should not exceed 600 mg twice daily. Norvir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily (please refer to the Norvir 80 mg/ml oral solution Summary of Product Characteristics).

For older children it may be feasible to substitute tablets for the maintenance dose of the oral solution.

Dosage conversion from oral solution to tablets for children

Oral solution dose	Tablet dose
175 mg (2.2 ml) twice daily	200 mg in the morning and 200 mg in the evening
350 mg (4.4 ml) twice daily	400 mg in the morning and 300 mg in the evening
437.5 mg (5.5 ml) twice daily	500 mg in the morning and 400 mg in the evening
525 mg (6.6 ml) twice daily	500 mg in the morning and 500 mg in the evening

Norvir is not recommended in children below 2 years of age due to lack of data on safety and efficacy.

Renal impairment: Currently, there are no data specific to this patient population and therefore specific dosage recommendations cannot be made. The renal clearance of ritonavir is negligible, therefore, a decrease in the total body clearance is not expected in patients with renal impairment. Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment: Ritonavir is principally metabolised and eliminated by the liver. Pharmacokinetic data indicate that no dose adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2). Ritonavir should not be given to patients with severe hepatic impairment (see section 4.3).

Older people: Pharmacokinetic data indicated that no dose adjustment is necessary for older patients (see section 5.2).

4.3 Contraindications

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

When ritonavir is used as a pharmacokinetic enhancer of other PIs, consult the Summary of Product Characteristics of the co-administered protease inhibitor for contraindications.

Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent 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 medicinal product and risk of clinically significant adverse effects.

The enzyme-modulating effect of ritonavir may be dose dependent. For some products, contraindications may be more relevant when ritonavir is used as an antiretroviral agent than when ritonavir is used as a pharmacokinetic enhancer (e.g. rifabutin and voriconazole):

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased or decreased		
α_1 -Adrenoreceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 4.5).
Analgesics	Pethidine, piroxicam, propoxyphne	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.
Antiarrhythmics	Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, 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 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.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
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 Inhibitor	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
	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 section 4.4 and section 4.5 for coadministration of sildenafil in patients with erectile dysfunction.
	Vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
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 parenterally administered midazolam, see section 4.5.).

Ritonavir medicinal product level decreased

Herbal Preparation	St. John's Wort	Herbal preparations containing St John's wort (<i>Hypericum perforatum</i>) due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir (see section 4.5).
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4.4 Special warnings and precautions for use

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving Ritonavir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 Product Characteristics for the particular PI must be consulted.

Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer

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 haemophilic 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. Haemophilic patients should therefore be made aware of the possibility of increased bleeding.

Weight and metabolic parameters: An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. Lipid disorders should 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 Norvir 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 asymptomatic 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 jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

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, 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 (SPC) of the co-administered protease inhibitor. See also section 4.2.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8).

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. Norvir should be used with caution in such patients (see section 5.1).

Interactions with other medicinal products

Ritonavir dosed as an antiretroviral agent

The following Warnings and Precautions should be considered when ritonavir is used as an antiretroviral agent. When ritonavir is used as a pharmacokinetic enhancer at the 100 mg and 200 mg level it cannot be assumed that the following warnings and precautions will also apply. When ritonavir is used as a pharmacokinetic enhancer, full details on the warnings and precautions relevant to that particular PI must be considered, therefore the Summary of Product Characteristics, section 4.4, for the particular PI must be consulted to determine if the information below is applicable.

PDE5 inhibitors: Particular caution should be used when prescribing sildenafil or tadalafil for the treatment of erectile dysfunction in patients receiving ritonavir. Co-administration of ritonavir with these medicinal products is expected to substantially increase their concentrations and may result in associated adverse reactions such as hypotension and prolonged erection (see section 4.5).

Concomitant use of avanafil or vardenafil with ritonavir is contraindicated. Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see section 4.3).

HMG-CoA reductase inhibitors: The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A. 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 doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent of CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Digoxin: Particular caution should be used when prescribing ritonavir in patients taking digoxin since co-administration of ritonavir with digoxin is expected to increase digoxin levels. The increased digoxin levels may lessen over time (see section 4.5).

In patients who are already taking digoxin when ritonavir is introduced, the digoxin dose should be reduced to one-half of the patients' normal dose and patients need to be followed more closely than usual for several weeks after initiating co-administration of ritonavir and digoxin.

In patients who are already taking ritonavir when digoxin is introduced, digoxin should be introduced more gradually than usual. Digoxin levels should be monitored more intensively than usual during this period, with dose adjustments made, as necessary, based on clinical, electrocardiographic and digoxin level findings.

Ethinyl estradiol: Barrier or other non-hormonal methods of contraception should be considered when administering ritonavir at therapeutic or low doses as ritonavir is likely to reduce the effect and change the uterine bleeding profile when co-administered with estradiol-containing contraceptives.

Glucocorticoids: Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5).

Trazodone: Particular caution should be used when prescribing ritonavir in patients using trazodone. Trazodone is a CYP3A4 substrate and co-administration of ritonavir is expected to increase trazodone levels. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed in single dose interaction studies in healthy volunteers (see section 4.5)

Rivaroxaban: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding (see section 4.5).

Bedaquiline: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline Summary of Product Characteristics).

Ritonavir dosed as a pharmacokinetic enhancer

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

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

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 Norvir 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 decrease 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 (e.g. 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 NORVIR (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. Norvir 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 Atazanavir ¹	↑ 86% ↑ 2 fold	↑ 11 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 Reyataz Summary of Product Characteristics.					
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
	400 q12h	400 q12h	Ritonavir Indinavir ³ Ritonavir	↑ 72% ↔ ↔	ND ↑ 4 fold ↔
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. Ritonavir 100 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 hepatotoxicity, 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-study 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 NORVIR (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 (e.g., 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.					
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels					
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 NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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Alpha₁-Adrenoreceptor Antagonist

Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore contraindicated (see section 4.3).			
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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).			
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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 SPC 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).			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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 (including respiratory depression) 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.			

Antiarrhythmics

Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine and is therefore contraindicated (see section 4.3).			
Digoxin	0.5 single IV dose 0.4 single oral dose	300 q12h, 3 days 200 q12h, 13 days	↑ 86% ↑ 22%	ND ↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antiretroviral 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 theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.			

Anticancer agents

Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.			
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Anticoagulant

Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12h	↑ 9% ↓ 33%	↓ 9% ↔
<p>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.</p>				
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.			
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 C _{max} 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.				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir.			
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 antiretroviral 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- <i>O</i> -desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	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.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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.			
Bedaquiline	No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline Summary of Product Characteristics).			
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 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.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
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, pimozone	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozone 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).			
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Norvir and quetiapine is contraindicated as it may increase quetiapine-related toxicity.			
β2-agonist (long acting)				
Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol 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.			
Endothelin antagonists				
Bosentan	Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentrations (C _{max}) and area under the curve (AUC).			
Ergot Derivatives				
Dihydroergotamine, ergonovine, ergotamine, methylegonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3).			
GI motility agent				
Cisapride	Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride 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 NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
HCV Protease Inhibitor				
Simeprevir	200 qd	100 q12h	↑ 7.2-fold	↑ 4.7-fold
Ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition. It is not recommended to co-administer ritonavir with simeprevir.				
HMG Co-A Reductase Inhibitors				
Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, 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).				
Immunosuppressants				
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 (PDE5) inhibitors				
Avanafil	50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
Concomitant use of avanafil with ritonavir is 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 NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
Sildenafil	100, single dose	500 q12h	↑ 11-fold	↑ 4-fold
<p>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).</p>				
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
<p>The concomitant use of tadalafil for the treatment of erectile dysfunction 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).</p> <p>When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC or prescribing information</p>				
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
<p>Concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).</p>				

Sedatives/hypnotics

Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	<p>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 Norvir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of Norvir 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, Norvir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Norvir 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 Norvir 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.</p>			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
<p>Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3).</p>				
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
<p>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 (e.g., seizures), see section 4.3.</p>				
Alprazolam	1, single dose	200 q12h, 2 days 500 q12h, 10 days	↑2.5 fold ↓ 12%	↔ ↓ 16%
<p>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.</p>				
Buspirone	<p>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.</p>			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
<p>Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.</p>				
Smoke cessation				
Bupropion	150 150	100 q12h 600 q12h	↓ 22% ↓ 66%	↓ 21% ↓ 62%
<p>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 <i>in vitro</i>, 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.</p>				
Steroids				
Fluticasone propionate aqueous nasal spray	200 µg qd	100 q12h	↑ ~350-fold	↑ ~ 25-fold
<p>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 e.g., budesonide. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic</p>				

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C _{max}
	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 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a 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 comparison
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.

Ritonavir dosed as a pharmacokinetic enhancer

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

Proton pump inhibitors and H₂-receptor antagonists: proton pump inhibitors and H₂-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 Fertility, 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 Norvir 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.

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. HIV infected women should not breast-feed their infants under any circumstances to avoid transmission of HIV.

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 SPC of the specific co-administered PI.

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia) and fatigue/asthenia.

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.

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Decreased WBC, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils

Immune system disorders	Common	Hypersensitivity including urticaria, and face oedema
	Rare	Anaphylaxis
Metabolic and nutritional disorders	Common	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms)
	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very Common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance, vomiting, dyspepsia)
	Common	Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia and back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased

Renal and urinary disorders	Common	Increased urination, renal impairment (e.g. oliguria, elevated creatinine)
	Uncommon	Acute renal failure
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common	Fatigue including asthenia, flushing, feeling hot
	Common	Fever, weight loss
Investigations	Common	Increased amylase, decreased free and total thyroxin
	Uncommon	Increased glucose, increased magnesium, 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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in [Appendix V](#)**.

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 little inhibitory 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 than that 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 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. 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 official continuous 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 patients extensively pre-treated with nucleoside analogues and baseline CD4 cell counts ≤ 100 cells/ μ l 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/ μ l) 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.

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/m² every 12 hours co-administered with zidovudine 160 mg/m² every 8 hours and lamivudine 4 mg/kg every 12 hours. In intent to treat analyses, 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 naïve and naïve to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m² 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

Absorption:

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV-infected adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. The time to maximum concentration (T_{max}) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0.1 l/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosing schemes of ritonavir alone are shown in the table below. Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatin capsule under fed conditions.

	Ritonavir Dosing Regimen				
	100 mg once daily	100 mg twice daily ¹	200 mg once daily	200 mg twice daily	600 mg twice daily
C_{max} (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3	11.2 ± 3.6
C_{trough} (µg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2	3.7 ± 2.6
AUC _{12 or 24} (µg•h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48	77.5 ± 31.5
$t_{1/2}$ (h)	~5	~5	~4	~8	~3 to 5
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2	8.8 ± 3.2

¹ Values expressed as geometric means. Note: ritonavir was dosed after a meal for all listed regimens.

Effects of food on oral absorption:

Food slightly decreases the bioavailability of the Norvir tablet. Administration of a single 100 mg dose of Norvir tablet 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 single 600 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 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 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/m² twice daily to 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m²) 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/m²) declined with age with median values of 9.0 L/h/m² in children less than 3 months of age, 7.8 L/h/m² in children between 3 and 6 months of age and 4.4 L/h/m² 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 proteinuria were noted 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 (embryo lethality, 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 (embryo lethality, 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

Tablet:

Copovidone
Sorbitan laurate
Calcium hydrogen phosphate, anhydrous
Silica, colloidal anhydrous
Sodium stearyl fumarate

Film-coating:

Hypromellose
Titanium dioxide (E171)
Macrogols
Hydroxypropyl cellulose
Talc
Silica, colloidal anhydrous
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

Norvir tablets are supplied in white high density polyethylene (HDPE) bottles closed with polypropylene caps.

Three pack sizes are available for Norvir tablets:

- 1 bottle of 30 tablets
- 1 bottle of 60 tablets

- Multipack containing 90 (3 bottles of 30) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/005-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 1996

Date of latest renewal: 26 August 2006

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Film-coated tablets and powder for oral suspension

AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany

Powder for oral suspension only

AbbVie Logistics B.V., Zuiderzeelaan 53, 8017 JV Zwolle, The Netherlands

Oral solution

Aesica Queenborough Limited, Queenborough, Kent, ME11 5EL, United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The Marketing Authorisation Holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

NORVIR ORAL SOLUTION - Carton of multipack containing 450 ml (5 bottles of 90 ml) oral solution – including blue box

1. NAME OF THE MEDICINAL PRODUCT

Norvir 80 mg/ml oral solution
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 80 mg of ritonavir.

3. LIST OF EXCIPIENTS

Also contains: alcohol (43% by volume), polyoxyl 35 castor oil, propylene glycol, saccharin sodium, sunset yellow E110.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 450 ml (5 bottles of 90 ml) oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Do not refrigerate or freeze.

Use within the expiry date. Shake well before each use. If, after shaking, particles or precipitate can be seen in the solution, take the next dose and see your doctor about a fresh supply.

Avoid exposure to excessive heat. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Norvir 80 mg/ml oral solution

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

NORVIR ORAL SOLUTION – Carton containing 1 bottle of 90 ml oral solution with blue box

1. NAME OF THE MEDICINAL PRODUCT

Norvir 80 mg/ml oral solution
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 80 mg of ritonavir.

3. LIST OF EXCIPIENTS

Also contains: alcohol (43% by volume), polyoxyl 35 castor oil, propylene glycol, saccharin sodium, sunset yellow E110.

4. PHARMACEUTICAL FORM AND CONTENTS

90 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Do not refrigerate or freeze.

Use within the expiry date. Shake well before each use. If, after shaking, particles or precipitate can be seen in the solution, take the next dose and see your doctor about a fresh supply.

Avoid exposure to excessive heat. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Norvir 80 mg/ml oral solution

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

NORVIR ORAL SOLUTION - Bottle Label Text

1. NAME OF THE MEDICINAL PRODUCT

Norvir 80 mg/ml oral solution
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 80 mg of ritonavir.

3. LIST OF EXCIPIENTS

Also contains: alcohol (43% by volume), polyoxyl 35 castor oil, propylene glycol, saccharin sodium, sunset yellow E110.

4. PHARMACEUTICAL FORM AND CONTENTS

90 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Do not refrigerate or freeze.

Use within the expiry date. Shake well before each use. If, after shaking, particles or precipitate can be seen in the solution, take the next dose and see your doctor about a fresh supply.

Avoid exposure to excessive heat. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/001
EU/1/96/016/008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

NORVIR POWDER FOR ORAL SUSPENSION - Carton containing 30 sachets each containing 100mg ritonavir

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg powder for oral suspension
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 100 mg of ritonavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 sachets of powder for oral suspension
Carton also contains 1 mixing cup and 2 oral dosing syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg oral powder

MINIMUM PARTICULARS TO APPEAR ON SMALL PACKAGING UNITS

NORVIR POWDER FOR ORAL SUSPENSION - Sachet Label Text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Norvir 100 mg powder for oral suspension
ritonavir
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY UNIT

100 mg



PARTICULARS TO APPEAR ON THE OUTER PACKAGING

NORVIR FILM-COATED TABLETS - CARTON WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg ritonavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Norvir tablets should be taken with food.
The tablets should be swallowed whole and not chewed, broken or crushed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/005
EU/1/96/016/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

NORVIR FILM-COATED TABLETS - Bottle Label Text

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg ritonavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/005
EU/1/96/016/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

NORVIR FILM-COATED TABLETS - Multipack containing 90 (3 bottles of 30) film-coated tablets with blue box

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg ritonavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Norvir tablets should be taken with food.
The tablets should be swallowed whole and not chewed, broken or crushed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

NORVIR FILM-COATED TABLETS BOTTLE LABEL TEXT – 3 BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Norvir 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg ritonavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Norvir 80 mg/ml oral solution ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4..

What is in this leaflet:

1. What Norvir is and what it is used for
2. What you need to know before you take Norvir
3. How to take Norvir
4. Possible side effects
5. How to store Norvir
6. Contents of the pack and other information

1. What Norvir is and what it is used for

Norvir contains the active substance ritonavir. Norvir is a protease inhibitor used to control HIV infection. Norvir is used in combination with other anti-HIV medicines (antiretrovirals) to control your HIV infection.

Norvir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS. Norvir should not be administered to children younger than 2 years of age unless specifically directed by their doctor.

Norvir can be used at full dose on its own, or at lower doses (called booster doses) with other medicines. Your doctor will discuss with you the best combination of medicines for you.

2. What you need to know before you take Norvir

Do not take Norvir

- if you are allergic to ritonavir or any of the other ingredients of Norvir (see section 6).
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
 - amiodarone, bepridil, encainide, flecainide, propafenone, quinidine (used to correct irregular heartbeats);
 - dihydroergotamine, ergotamine (used to treat migraine headache);
 - ergonovine, methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion);
 - clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety);

- clozapine, pimozide, (used to treat abnormal thoughts or feelings);
- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
- pethidine, piroxicam, propoxyphene (used to relieve pain);
- cisapride (used to relieve certain stomach problems);
- rifabutin (used to prevent/treat certain infections)*;
- voriconazole (used to treat fungal infections)*;
- simvastatin, lovastatin (used to lower blood cholesterol);
- alfuzosin (used to treat enlarged prostate gland);
- fusidic acid (used to treat bacterial infections);
- sildenafil if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without this disease may use sildenafil for impotence (erectile dysfunction) under their doctor's supervision (see the section on **Other medicines and Norvir**);
- avanafil or vardenafil (used to treat erectile dysfunction);
- products containing St John's wort (*Hypericum perforatum*) as this may stop Norvir from working properly. St John's wort is often used in herbal medicines that you can buy yourself.

* Your doctor may decide that you can take rifabutin and/or voriconazole with a booster (lower dose) of Norvir but a full dose of Norvir must not be taken together with these two medicines.

If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Norvir. Often, there are other medicines you can take instead.

Also read the list of medicines under 'Other medicines and Norvir' for use with certain other medicines which require special care.

Warnings and precautions

Talk to your doctor before taking Norvir.

Important information

- If Norvir is taken in combination with other antiretroviral medicines, it is important that you also carefully read the leaflets that are provided with these other medicines. There may be additional information in those leaflets about situations when Norvir should be avoided. If you have any further questions about Norvir (ritonavir) or the other medicines prescribed, please ask your doctor or pharmacist.
- Norvir is not a cure for HIV infection or AIDS.
- People taking Norvir may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of your doctor while taking Norvir.
- You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

Tell your doctor if you have/had:

- A history of **liver disease**.
- **Hepatitis B or C** and are being treated with a combination of antiretroviral agents, as you are at a greater risk of a severe and potentially life threatening reaction because of the effect on the liver. Regular blood tests may be required to check your liver is working properly.
- **Haemophilia**, as there have been reports of increased bleeding in patients with haemophilia who are taking this type of medicine (protease inhibitors). The reason for this is not known.

You may need additional medicine to help your blood clot (factor VIII), in order to control any bleeding.

- **Erectile Dysfunction**, as the medicines used to treat erectile dysfunction can cause hypotension and prolonged erection.
- **Diabetes**, as there have been reports of worsening of or the development of diabetes (diabetes mellitus) in some patients taking protease inhibitors.
- **Kidney (renal) disease**, since your doctor may need to check the dose of your other medicines (such as protease inhibitors).

Tell your doctor if you experience:

- **Diarrhoea or vomiting** that is not improving (persistent), as this may reduce how well the medicines you are taking work.
- **Feeling sick** (nausea), **vomiting** or have **stomach pain**, because these may be signs of inflammation of the pancreas (pancreatitis). Some patients taking Norvir can develop serious problems with their pancreas. Tell your doctor as soon as possible if this applies to you.
- **Symptoms of infection** – inform your doctor immediately. Some patients with advanced HIV infection (AIDS) who then start anti-HIV treatment may develop the symptoms of infections they have had in the past even if they didn't know they had had them. It is believed that this happens because the body's immune response improves and helps the body to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty moving, tell your doctor, as this may be a sign of a problem that can destroy bone (osteonecrosis). Some patients taking a number of antiretroviral medicines may develop this disease.
- **Muscle pain, tenderness or weakness**, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious. (See section 4 **Possible side effects**)
- **Dizziness, lightheadedness, fainting spells or abnormal heartbeat**. Some patients taking Norvir may experience changes in the electrocardiogram (ECG). Tell your doctor if you have a heart defect or conduction defect.
- If you have any other health concerns, discuss these with your doctor as soon as you can.

Norvir is not recommended in children below 2 years of age

Other medicines and Norvir

There are some medicines you cannot take at all with Norvir. These are listed earlier in Section 2, under 'Do not take Norvir'. There are some other medicines that can only be used under certain circumstances as described below. Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

The following warnings apply when Norvir is taken as a full dose. However, these warnings may also apply when Norvir is used in lower doses (a booster) with other medicines.

Tell your doctor if you are taking any of the medicines listed below, as special care should be taken.

- **Sildenafil or tadalafil** for impotence (erectile dysfunction).
The dose and/or frequency of use of these medicines may need to be reduced to avoid hypotension and prolonged erection. You must not take Norvir with sildenafil if you suffer from pulmonary arterial hypertension (see also section 2. **Before you take Norvir**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.
- **Digoxin** (heart medicine). Your doctor may need to adjust the dose of digoxin and monitor you while you are taking digoxin and Norvir in order to avoid heart problems.
- **Hormonal contraceptives** containing ethinyl oestradiol as Norvir may reduce the effectiveness of these medicines. It is recommended that a condom or other non-hormonal method of contraception is used instead. You may also notice irregular uterine bleeding if you are taking this type of hormonal contraceptive with Norvir.
- **Atorvastatin or rosuvastatin** (for high cholesterol) as Norvir may raise the blood levels of these medicines. Talk to your doctor before you take any cholesterol-reducing medicines with Norvir (see also ‘**Do not take Norvir**’ above).
- **Steroids** (e.g. dexamethasone, fluticasone propionate, prednisolone) as Norvir may raise the blood levels of these medicines which may lead to Cushing’s syndrome (development of a rounded face) and reduce production of the hormone cortisol. Your doctor may wish to reduce the steroid dose or monitor your side effects more closely.
- **Trazodone** (a medicine for depression) as, unwanted effects like nausea, dizziness, low blood pressure and fainting can occur when taken with Norvir.
- **Rifampicin and saquinavir** (used for tuberculosis and HIV, respectively) as serious liver damage can occur when taken with Norvir.
- **Bosentan** (used for pulmonary arterial hypertension) as Norvir may increase the blood levels of this medicine

There are medicines that may not mix with Norvir because their effects could increase or decrease when taken together. In some cases your doctor may need to perform certain tests, change the dose or monitor you regularly. This is why you should tell your doctor if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention these:

- amphetamine or amphetamine derivatives;
- antibiotics (e.g. erythromycin, clarithromycin);
- anticancer treatments (e.g. dasatinib, nilotinib, vincristine, vinblastine);
- anticoagulants (e.g. rivaroxaban, warfarin)
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole);
- antihistamines (e.g. loratidine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors and Non-nucleoside reverse transcriptase inhibitors (NNRTI);
- anti-tuberculosis medicine (bedaquiline);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (simeprevir);
- anxiety medicine, buspirone;
- asthma medicine, theophylline, salmeterol;
- atovaquone, a medicine used to treat a certain type of pneumonia and malaria;
- buprenorphine, a medicine used for the treatment of chronic pain;
- bupropion, a medicine used to help you stop smoking;
- epilepsy medicines (e.g. carbamazepine, divalproex, lamotrigine, phenytoin);

- heart medicines (e.g. digoxin, disopyramide, mexiletine and calcium channel antagonists such as amlodipine, diltiazem and nifedipine);
- immune system (e.g. cyclosporine, tacrolimus, everolimus);
- morphine and morphine-like medicines used to treat severe pain (e.g. methadone, fentanyl);
- sleeping pills (e.g. alprazolam, zolpidem) and also midazolam administered by injection;
- tranquillisers (e.g. haloperidol, risperidone, thioridazine);
- colchicine, a treatment for gout.

Norvir should not be used with disulfiram (a medicine used to treat alcoholism) and metronidazole (a medicine used for certain bacterial infections) as they can interact with the alcohol contained in the oral solution.

There are some medicines you cannot take at all with Norvir. These are listed earlier in section 2, under 'Do not take Norvir'.

Taking Norvir with food and drink

Norvir should preferably be taken with food. The bitter taste of Norvir oral solution may be better if it is mixed with chocolate milk. Do not mix with water. Eating salty food or drinking fluids before or after taking Norvir oral solution can help clear the aftertaste from your mouth.

Pregnancy and breast-feeding

If you think you are pregnant or you are planning to become pregnant, it is very important that you discuss this with your doctor.

There is very little information on the use of ritonavir (the active ingredient in Norvir) during pregnancy. In general, the pregnant mothers received ritonavir after the first three months of pregnancy at a lower dose (booster) along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

It is not known if Norvir passes into breast milk. To avoid transmitting the infection, mothers with HIV should not breast feed their babies.

Driving and using machines

Norvir can cause sleepiness and dizziness. If you are affected do not drive or use machinery.

Important information about some of the ingredients of Norvir

Norvir contains 43% v/v alcohol and 26.0% v/v propylene glycol. Each 1 ml of Norvir oral solution contains 344.0 mg of alcohol and 265.7 mg of propylene glycol. Alcohol and propylene glycol are potentially harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. They may modify or increase the effect of other medicines.

Norvir contains polyoxyl 35 castor oil which may cause stomach upset and diarrhoea.

Norvir contains the colouring agent sunset yellow (E110) which may cause allergic reactions.

3. How to take Norvir

Always take Norvir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. It is taken by mouth usually two times every day. Norvir should preferably be taken with food.

Shake the bottle well before each use. If, after shaking, particles or solids can be seen in the solution, take the next dose and see your doctor or pharmacist about a fresh supply.

Recommended doses of Norvir are:

- if Norvir is used to boost the effects of other anti-HIV medicines, the typical dose for adults is 1.25 to 2.5 ml once or twice daily. For more detailed dose recommendations, including those for children, see the Package Leaflet of the anti-HIV medicines Norvir is given in combination with.
- if your doctor prescribes a full dose, adults may be started on a dose of 3.75 ml in the morning and 3.75 ml 12 hours later, gradually increasing over a period of up to 14 days to the full dose of 7.5 ml twice daily. Children (2 – 12 years of age) will start with a dose smaller than this and continue up to the maximum allowed for their size.

Your doctor will advise you on the dosage to be taken.

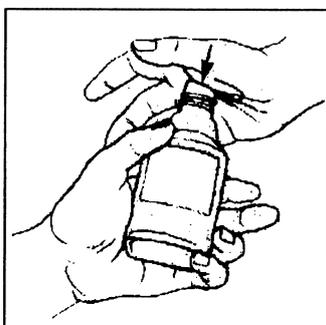
Like all anti-HIV medicines, Norvir should be taken every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking Norvir, tell your doctor straight away. During episodes of diarrhoea your doctor may decide that extra monitoring is needed.

Always keep enough Norvir on hand so you don't run out. When you travel or need to stay in the hospital, make sure you have enough Norvir to last until you can get a new supply.

Norvir oral solution has a lingering aftertaste. You can take it alone or mix it with chocolate milk to improve the taste. Mix only one dose at a time, and be sure to take the whole dose right away. **Do not mix** Norvir with anything else without talking to your doctor or pharmacist. **Do not mix** with water. Eating salty foods or drinking fluids before or after taking Norvir oral solution may help clear the aftertaste from your mouth.

How do I measure the correct dose of the solution?

Open the childproof cap by pushing down on it with your palm and twisting it anti-clockwise, or in the direction of the arrow.



1 dosing syringe is included in the 1 bottle carton of Norvir oral solution and
5 dosing syringes are included in the 5 bottle carton of Norvir oral solution

Ask your pharmacist for instructions on how to use the syringe correctly.

After each dose of Norvir, separate the plunger and the syringe. Wash the plunger and the syringe with dish soap and warm water as soon as you can; you may soak both in the soapy water for up to 15 minutes. Rinse the syringe and plunger with clean water. Put the syringe back together and draw up and expel tap water a few times to rinse. Let the syringe dry completely before you use that syringe for dosing.

If you take more Norvir than you should

Numbness, tingling, or a “pins and needles” sensation may occur if you take too much Norvir. If you realise you have taken more Norvir than you were supposed to, contact your doctor or the Accident and Emergency Department of your nearest hospital straight away.

If you forget to take Norvir

If you miss a dose, take the missed dose as soon as possible. If it is nearly time for the next dose, just take that one. Do not take a double dose to make up for a forgotten dose.

If you stop taking Norvir

Even if you feel better, do not stop taking Norvir without talking to your doctor. Taking Norvir as recommended should give you the best chance of delaying resistance to the medicines.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, Norvir can cause side effects, although not everybody gets them. Also, the side effects of Norvir when used with other antiretroviral medicines are dependent on the other medicines. So it is important that you carefully read the side effects section of the leaflets that are provided with these other medicines.

The frequency of possible side effects listed below is defined using the following convention:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data.

Very common side effects:

- upper or lower stomach ache
- vomiting
- diarrhoea (may be severe)
- feeling sick (nausea)
- flushing, feeling hot
- headache
- dizziness`
- pain in the throat
- a tingling sensation or numbness in the hands, feet or around the lips and mouth
- feeling weak/tired
- bad taste in the mouth
- damage to the nerves that can cause weakness and pain
- itching

- cough
- upset stomach or indigestion
- rash
- joint pain and back pain

Common side effects:

- allergic reactions including skin rashes (may be red, raised, itchy), severe swelling of the skin and other tissues
- inability to sleep (insomnia)
- anxiety
- increase in cholesterol
- increase in triglycerides
- gout
- stomach bleeding
- inflammation of the liver and yellowing of skin or whites of the eyes
- increase in urination
- reduced kidney function
- seizures (fits)
- low levels of blood platelets
- thirst (dehydration)
- abnormally heavy periods
- wind (flatulence)
- loss of appetite
- mouth ulcer
- muscle aches (pain), tenderness or weakness
- fever
- weight loss
- laboratory test results: changes in blood test results (such as blood chemistry and blood count)
- confusion
- difficulty paying attention
- fainting
- blurred vision
- swelling of the hands and feet
- high blood pressure
- low blood pressure and feeling faint when getting up
- coldness in the hands and feet
- acne

Uncommon side effects:

- heart attack
- diabetes
- kidney failure

Rare side effects:

- severe or life threatening skin reaction including blisters (Stevens Johnson syndrome, toxic epidermal necrolysis)
- serious allergic reaction (anaphylaxis)
- high levels of sugar in the blood

Tell your doctor if you feel sick (nauseous), are vomiting, or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your doctor if you experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. See also section 2 **Before you take Norvir**.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Abnormal liver function tests, hepatitis (inflammation of the liver), and rarely jaundice, have been reported in patients taking Norvir. Some people had other illnesses or were taking other medicines. People with liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly when taking medicines to lower cholesterol in combination with antiretroviral therapy, including protease inhibitors and

nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis). In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop taking the medicine, contact your doctor as soon as possible or go to the Accident and Emergency Department of your nearest hospital.

Inform your doctor as soon as possible if you experience any symptoms that suggest an allergic reaction after taking Norvir such as rash, hives or breathing difficulties.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, contact your doctor, pharmacist, Accident and Emergency department or if it is urgent get immediate medical help.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Norvir

Keep this medicine out of the sight and reach of children.

Do not use Norvir oral solution after the expiry date on the bottle. The expiry date refers to the last day of the month.

Bottles of Norvir oral solution should be stored below 25°C. Do not store Norvir oral solution in the refrigerator, or in extreme heat or cold (such as in a car during hot or very cold weather, or in your freezer).

It is important to keep Norvir in the bottle it came in. Don't transfer it to any other container.

6. Contents of the pack and other information

What Norvir contains

- The active substance is ritonavir. Each ml of Norvir contains 80 mg ritonavir.
- The other ingredients are alcohol, purified water, polyoxyl 35 castor oil, propylene glycol, saccharin sodium, anhydrous citric acid, peppermint oil, creamy caramel flavouring and sunset yellow E110.

What Norvir looks like and contents of the pack

Norvir oral solution comes in an amber bottle containing 90 ml of liquid.

Two pack sizes are available for Norvir oral solution:

- 1 bottle of 90 ml plus one 7.5 ml dosing syringe.
- multipacks comprising 5 bottles each containing 90 ml oral solution (450 ml) plus five 7.5 ml dosing syringes.

Not all pack sizes may be marketed.

Norvir is also supplied as a capsule containing 100 mg of ritonavir, and as a film-coated tablet containing 100 mg ritonavir.

Marketing Authorisation Holder

AbbVie Ltd
Maidenhead
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United Kingdom

Manufacturer

Aesica Queenborough Limited
Queenborough
Kent ME11 5EL
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

Package leaflet: Information for the user

Norvir 100 mg powder for oral suspension ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you or your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Norvir is and what it is used for
2. What you need to know before you or your child take Norvir
3. How to take Norvir
4. Possible side effects
5. How to store Norvir
6. Contents of the pack and other information

1. What Norvir is and what it is used for

Norvir contains the active substance ritonavir. Norvir is a protease inhibitor used to control HIV infection. Norvir is used in combination with other anti-HIV medicines (antiretrovirals) to control your HIV infection. Your doctor will discuss with you the best combination of medicines for you

Norvir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS.

2. What you need to know before you or your child take Norvir

Do not take Norvir

- if you are allergic to ritonavir or any of the other ingredients of Norvir (see section 6).
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
 - amiodarone, bepridil, encainide, flecainide, propafenone, quinidine (used to correct irregular heartbeats);
 - dihydroergotamine, ergotamine (used to treat migraine headache);
 - ergonovine, methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion);
 - clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety);
 - clozapine, pimozide, (used to treat abnormal thoughts or feelings);
 - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
 - pethidine, piroxicam, propoxyphene (used to relieve pain);
 - cisapride (used to relieve certain stomach problems);

- rifabutin (used to prevent/treat certain infections)*;
- voriconazole (used to treat fungal infections)*;
- simvastatin, lovastatin (used to lower blood cholesterol);
- alfuzosin (used to treat enlarged prostate gland);
- fusidic acid (used to treat bacterial infections);
- sildenafil if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without this disease may use sildenafil for impotence (erectile dysfunction) under their doctor's supervision (see the section on **Other medicines and Norvir**);
- avanafil or vardenafil (used to treat erectile dysfunction);
- products containing St John's wort (*Hypericum perforatum*) as this may stop Norvir from working properly. St John's wort is often used in herbal medicines that you can buy yourself.

* Your doctor may decide that you can take rifabutin and/or voriconazole with a booster (lower dose) of Norvir but a full dose of Norvir must not be taken together with these two medicines.

If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Norvir.

Also read the list of medicines under 'Other medicines and Norvir' for use with certain other medicines which require special care.

Warnings and precautions

Talk to your doctor before taking Norvir.

Important information

- If Norvir is taken in combination with other antiretroviral medicines, it is important that you also carefully read the leaflets that are provided with these other medicines. There may be additional information in those leaflets about situations when Norvir should be avoided. If you have any further questions about Norvir (ritonavir) or the other medicines prescribed, please ask your doctor or pharmacist.
- Norvir is not a cure for HIV infection or AIDS.
- People taking Norvir may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of your doctor while taking Norvir.
- You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

Tell your doctor if you have/had:

- A history of **liver disease**.
- **Hepatitis B or C** and are being treated with a combination of antiretroviral agents, as you are at a greater risk of a severe and potentially life threatening reaction because of the effect on the liver. Regular blood tests may be required to check your liver is working properly.
- **Haemophilia**, as there have been reports of increased bleeding in patients with haemophilia who are taking this type of medicine (protease inhibitors). The reason for this is not known. You may need additional medicine to help your blood clot (factor VIII), in order to control any bleeding.
- **Erectile dysfunction**, as the medicines used to treat erectile dysfunction can cause hypotension and prolonged erection.

- **Diabetes**, as there have been reports of worsening of or the development of diabetes (diabetes mellitus) in some patients taking protease inhibitors.
- **Kidney (renal) disease**, since your doctor may need to check the dose of your other medicines (such as protease inhibitors).

Tell your doctor if you experience:

- **Diarrhoea or vomiting** that is not improving (persistent), as this may reduce how well the medicines you are taking work.
- **Feeling sick** (nausea), **vomiting** or have **stomach pain**, because these may be signs of inflammation of the pancreas (pancreatitis). Some patients taking Norvir can develop serious problems with their pancreas. Tell your doctor as soon as possible if this applies to you.
- **Symptoms of infection** – inform your doctor immediately. Some patients with advanced HIV infection (AIDS) who then start anti-HIV treatment may develop the symptoms of infections they have had in the past even if they didn't know they had had them. It is believed that this happens because the body's immune response improves and helps the body to fight these infections.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty moving, tell your doctor, as this may be a sign of a problem that can destroy bone (osteonecrosis). Some patients taking a number of antiretroviral medicines may develop this disease.
- **Muscle pain, tenderness or weakness**, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious. (See section 4 **Possible side effects**)
- **Dizziness, lightheadedness, fainting spells or abnormal heartbeat**. Some patients taking Norvir may experience changes in the electrocardiogram (ECG). Tell your doctor if you have a heart defect or conduction defect.
- If you have any other health concerns, discuss these with your doctor as soon as you can.

Children and adolescents

Norvir is not recommended in children below 2 years of age.

Other medicines and Norvir

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. There are some medicines you cannot take at all with Norvir. These are listed earlier in Section 2, under 'Do not take Norvir'. There are some other medicines that can only be used under certain circumstances as described below. The following warnings apply when Norvir is taken as a full dose. However, these warnings may also apply when Norvir is used in lower doses (a booster) with other medicines.

Tell your doctor if you are taking any of the medicines listed below, as special care should be taken.

- **Sildenafil or tadalafil** for impotence (erectile dysfunction).
The dose and/or frequency of use of these medicines may need to be reduced to avoid hypotension and prolonged erection. You must not take Norvir with sildenafil if you suffer

- from pulmonary arterial hypertension (see also section 2. **Before you take Norvir**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.
- **Digoxin** (heart medicine). Your doctor may need to adjust the dose of digoxin and monitor you while you are taking digoxin and Norvir in order to avoid heart problems.
 - **Hormonal contraceptives** containing ethinyl oestradiol as Norvir may reduce the effectiveness of these medicines. It is recommended that a condom or other non-hormonal method of contraception is used instead. You may also notice irregular uterine bleeding if you are taking this type of hormonal contraceptive with Norvir.
 - **Atorvastatin or rosuvastatin** (for high cholesterol) as Norvir may raise the blood levels of these medicines. Talk to your doctor before you take any cholesterol-reducing medicines with Norvir (see also '**Do not take Norvir**' above).
 - **Steroids** (e.g. dexamethasone, fluticasone propionate, prednisolone) as Norvir may raise the blood levels of these medicines which may lead to Cushing's syndrome (development of a rounded face) and reduce production of the hormone cortisol. Your doctor may wish to reduce the steroid dose or monitor your side effects more closely.
 - **Trazodone** (a medicine for depression) as, unwanted effects like nausea, dizziness, low blood pressure and fainting can occur when taken with Norvir.
 - **Rifampicin and saquinavir** (used for tuberculosis and HIV, respectively) as serious liver damage can occur when taken with Norvir.
 - **Bosentan** (used for pulmonary arterial hypertension) as Norvir may increase the blood levels of this medicine

There are medicines that may not mix with Norvir because their effects could increase or decrease when taken together. In some cases your doctor may need to perform certain tests, change the dose or monitor you regularly. This is why you should tell your doctor if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention these:

- amphetamine or amphetamine derivatives;
- antibiotics (e.g. erythromycin, clarithromycin);
- anticancer treatments (e.g. dasatinib, nilotinib, vincristine, vinblastine);
- anticoagulants (e.g. rivaroxaban, warfarin)
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nefazadone, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole);
- antihistamines (e.g. loratadine, fexofenadine);
- antiretroviral medicines, including HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir), non-nucleoside reverse transcriptase inhibitors (NNRTI) (delavirdine, efavirenz, nevirapine), and others (didanosine, maraviroc, raltegravir, zidovudine);
- anti-tuberculosis medicine (bedaquiline);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (simeprevir);
- anxiety medicine, buspirone;
- asthma medicine, theophylline, salmeterol;
- atovaquone, a medicine used to treat a certain type of pneumonia and malaria;
- buprenorphine, a medicine used for the treatment of chronic pain;
- bupropion, a medicine used to help you stop smoking;
- epilepsy medicines (e.g. carbamazepine, divalproex, lamotrigine, phenytoin);
- heart medicines (e.g. disopyramide, mexiletine and calcium channel antagonists such as amlodipine, diltiazem and nifedipine);
- immune system medicines (e.g. cyclosporine, tacrolimus, everolimus);
- morphine and morphine-like medicines used to treat severe pain (e.g. methadone, fentanyl);
- sleeping pills (e.g. alprazolam, zolpidem) and also midazolam administered by injection;
- tranquillisers (e.g. haloperidol, risperidone, thioridazine);

- colchicine, a treatment for gout.

There are some medicines you cannot take at all with Norvir. These are listed earlier in section 2, under 'Do not take Norvir'.

Taking Norvir with food and drink

See section 3.

Pregnancy and breast-feeding

If you think you are pregnant or you are planning to become pregnant, it is very important that you discuss this with your doctor.

There is very little information on the use of ritonavir (the active ingredient in Norvir) during pregnancy. In general, pregnant mothers received ritonavir after the first three months of pregnancy at a lower dose (booster) along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

It is not known if Norvir passes into breast milk. To avoid transmitting the infection, mothers with HIV should not breast feed their babies.

Driving and using machines

Norvir can cause dizziness. If you are affected do not drive or use machinery.

3. How to take Norvir

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Take this medicine one or two times a day every day with food.

For doses of exactly 100 mg amounts (100, 200, 300, 400, 500, or 600 mg) pour the entire content of each sachet over soft food (apple sauce or vanilla pudding) or mix with a small amount of liquid (water, chocolate milk, or infant formula) and consume entire serving.

For doses less than 100 mg amounts or doses between 100 mg amounts, the content of the entire sachet is to be mixed with a liquid and then dosed by the appropriate mL volume as told to you by your doctor using the oral dosing syringe.

For administration using a feeding tube follow the instructions in section 'How do I take the correct dose of Norvir powder for oral suspension mixed with liquid?' **Use water to mix the medicine** and follow the feeding tube instructions to administer the medicine.

Recommended doses of Norvir are:

- if Norvir is used to boost the effects of other anti-HIV medicines, the typical dose for adults is 1 or 2 sachets once or twice daily. For more detailed dose recommendations, including those for children, see the Package Leaflet of the anti-HIV medicines Norvir is given in combination with.
- if your doctor prescribes a full dose, adults may be started on a dose of 3 sachets in the morning and 3 sachets 12 hours later, gradually increasing over a period of up to 14 days to the full dose of 6 sachets twice daily. Children (2 – 12 years of age) will start with a dose smaller than this and continue up to the maximum allowed for their size.

Your doctor will advise you on the dosage to be taken.

Norvir should be taken every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking Norvir, tell your doctor straight away. During episodes of diarrhoea your doctor may decide that extra monitoring is needed.

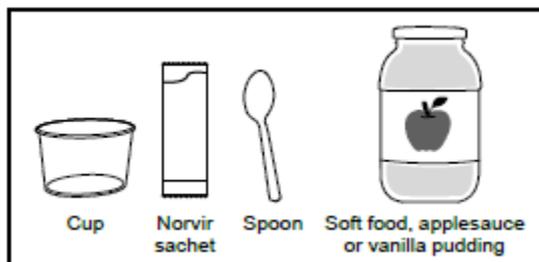
Always keep enough Norvir on hand so you don't run out. When you travel or need to stay in the hospital, make sure you have enough Norvir to last until you can get a new supply.

Norvir powder for oral suspension has a lingering aftertaste. Eating peanut butter, hazelnut chocolate spread, or black currant syrup immediately after taking the medication may help clear the aftertaste from your mouth.

Prepare only one dose at a time using the correct number of sachets. When mixing the powder with food or liquid, be sure to take the whole dose within 2 hours. Do not mix Norvir with anything else without talking to your doctor or pharmacist.

How do I take the correct dose of Norvir powder for oral suspension mixed with food (full sachet)?

Follow the instructions below:



Step 1. Before mixing dose of Norvir, collect the following supplies: (see Figure 1).

Step 2. Check prescription for number of sachets or call your doctor or pharmacist.

Figure 1



Step 3. Put a small serving of soft food (applesauce or vanilla pudding) in a cup (see Figure 2).

Figure 2

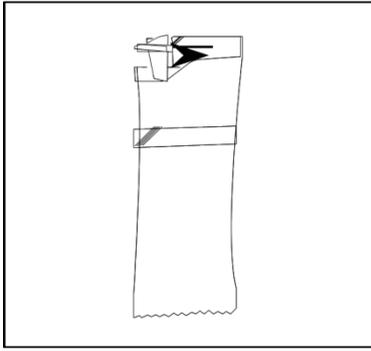


Figure 3

Step 4. Tear open sachet (see Figure 3).

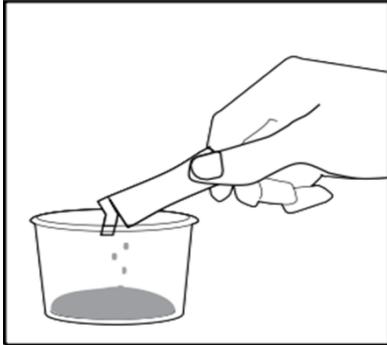


Figure 4

Step 5. Pour ALL powder from sachet onto food (see Figure 4).

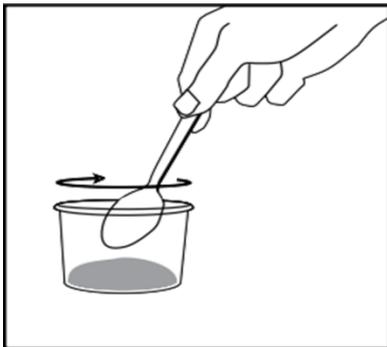


Figure 5

Step 6. Mix thoroughly (see Figure 5).

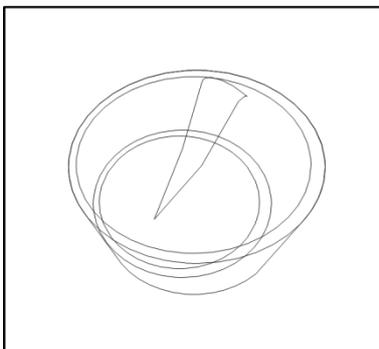


Figure 6

Step 7. Feed serving to patient.

Step 8. ENTIRE serving must be eaten (see Figure 6). If **powder residue** is left, add more spoonfuls of food and serve to patient. *Use within 2 hours.*

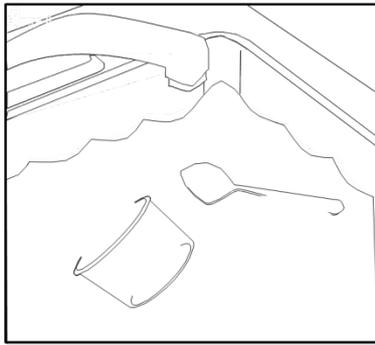


Figure 7

Step 9. Place empty sachet in rubbish. Wash and dry preparation area. Immediately wash the spoon and cup in warm water and dish soap (see Figure 7). Rinse and allow to air dry.

How do I take the correct dose of Norvir powder for oral suspension mixed with liquid?

Follow the instructions below:

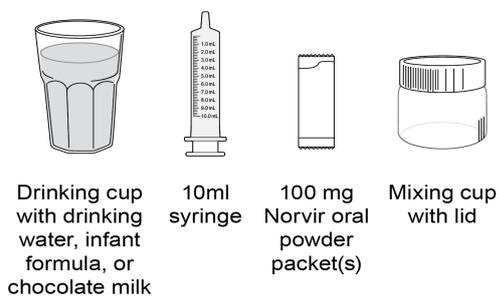


Figure 1

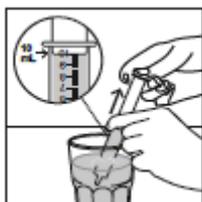
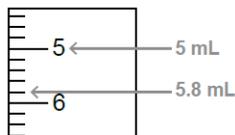


Figure 2

What you need

Before mixing a dose of Norvir, collect the items shown in Figure 1.

You may need more than 1 sachet for each dose. Check the prescription label on the carton or call your doctor or pharmacist if you are not sure. If you do need more than 1 sachet, repeat all the steps with each sachet.

Using the syringe

Reading the scale

- Each millilitre (mL) is shown as a number with a big line.
- Each 0.2 mL is shown as a smaller line between the numbers.

Check the syringe before each use

You will need to use a new syringe if:

- you cannot clean the syringe
- you cannot read the scale
- you cannot move the plunger
- the syringe is damaged or leaking.

Step 1. Fill the syringe

- Push the plunger all the way into syringe.
- Place the syringe tip into the liquid.
- Slowly pull the plunger back to the 10 mL mark on the syringe (see Figure 2).

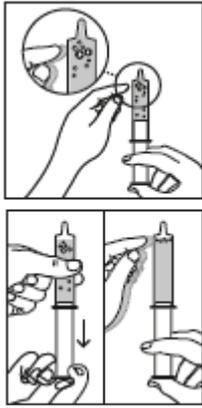


Figure 3

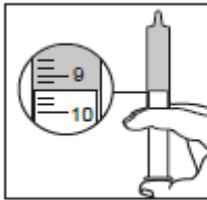


Figure 4

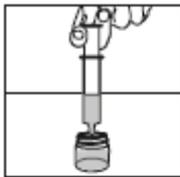


Figure 5

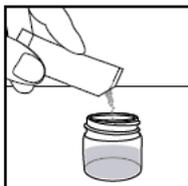


Figure 6

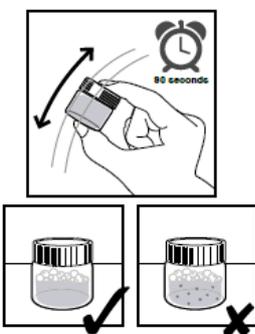


Figure 7

Step 2. Move any bubbles to the tip of the syringe

- a. Hold the syringe with the tip pointing up.
- b. Tap the syringe with your other hand. This will move any bubbles to the tip.
- c. Pull the plunger down.
Be careful not to pull the plunger out.
- d. Tap the syringe again. This will help to break up the bubbles and make sure they are all at the tip (see Figure 3).

Step 3. Measure the liquid

- a. Keep the syringe pointed up.
- b. Slowly push the plunger up until the top of the plunger is at 9.4 mL - this will remove any bubbles from the syringe (see Figure 4).

Step 4. Empty the syringe

- a. Slowly push the plunger to empty the liquid from the syringe into the mixing cup (see Figure 5).

Step 5. Pour the powder into the cup

- a. Tear open the sachet.
- b. Pour all of the powder into the mixing cup.
- c. Check if the sachet is empty.

Be careful not to spill any powder outside of the mixing cup (see Figure 6).

Step 6. Mix the powder and liquid

- a. Tightly screw on the lid and keep shaking the mixing cup hard for at least 90 seconds until all the lumps have gone.
- b. Check for any lumps of powder. If there are still lumps, keep shaking until they have all gone.
- c. The liquid may look cloudy - this is okay.
- d. Let the liquid stand for 10 minutes and most of the bubbles will disappear.
- e. You may see some small bubbles on top of the liquid - this is also okay (see Figure 7).

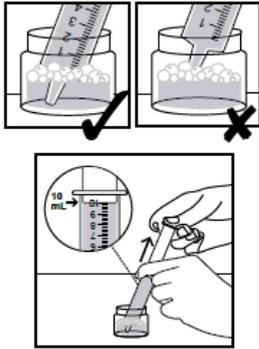


Figure 8

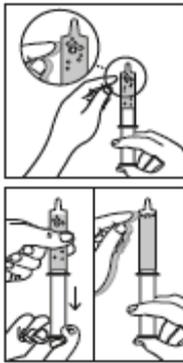


Figure 9

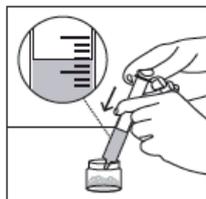


Figure 10

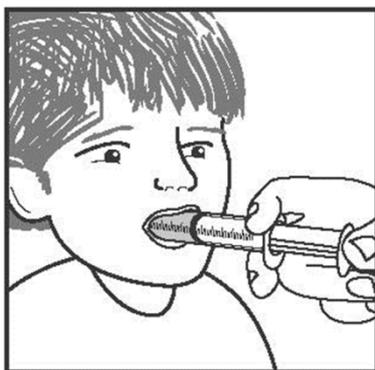


Figure 11

Step 7. Fill the syringe

- a. Push the plunger completely into the syringe.
- b. Place the syringe tip at the bottom of the mixing cup.
- c. Slowly pull the plunger back to the 10 mL mark - try not to pull any bubbles into the syringe (see Figure 8).

Step 8. Remove any bubbles

- a. Hold the syringe with the tip pointing up.
- b. Tap the syringe with your other hand. This will move any bubbles to the tip.
- c. Pull the plunger down. Be careful not to pull the plunger out.
- d. Tap the syringe again to break up the bubbles so they are all at the tip (see Figure 9).
- e. Slowly push the plunger until you see a small amount of liquid at the tip of the syringe.
- f. If there are any large air bubbles, empty the liquid from the syringe into the mixing cup and start again from Step 7.

Step 9. Measure the dose

- a. Check the prescription label on the carton for the dose in mL. If you are not sure, call your doctor or pharmacist.
- b. Point the syringe into the mixing cup and slowly push the plunger to the correct mL for the dose (see Figure 10).
- c. If you push out too much liquid, start again from Step 7. Be careful not to spill the liquid outside of the mixing cup.

Step 10. Give the medicine to the patient

- a. Place the syringe tip against the inside of the patient's cheek.
- b. Slowly push the plunger to give all of the dose (see Figure 11).
- c. Give the patient the full dose within 2 hours of opening the sachet.

Step 11. (If required)

If you need to use more than one sachet, repeat the process from the beginning.

Step 12. After you have finished

- a. Place the empty sachet and any left over medicine from the mixing cup into a rubbish bag.
- b. Remove the plunger from the syringe.
- c. Hand wash the syringe, plunger, and mixing cup and lid in warm water and dish soap. Rinse with water and allow to air dry. Do not wash these in the dishwasher.
- d. Wash and dry the area used to mix the medicine.

If you take more Norvir than you should

Numbness, tingling, or a “pins and needles” sensation may occur if you take too much Norvir. If you realise you have taken more Norvir than you were supposed to, contact your doctor or the Accident and Emergency Department of your nearest hospital straight away.

If you forget to take Norvir

If you miss a dose, take the missed dose as soon as possible. If it is nearly time for the next dose, just take that one. Do not take a double dose to make up for a forgotten dose.

If you stop taking Norvir

Even if you feel better, do not stop taking Norvir without talking to your doctor. Taking Norvir as recommended should give you the best chance of delaying resistance to the medicines.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, Norvir can cause side effects, although not everybody gets them. Also, the side effects of Norvir when used with other antiretroviral medicines are dependent on the other medicines. So it is important that you carefully read the side effects section of the leaflets that are provided with these other medicines.

Very common side effects (affects more than 1 user in 10):

- upper or lower stomach ache
- vomiting
- diarrhoea (may be severe)
- feeling sick (nausea)
- flushing, feeling hot
- headache
- dizziness`
- pain in the throat
- a tingling sensation or numbness in the hands, feet or around the lips and mouth
- feeling weak/tired
- bad taste in the mouth
- damage to the nerves that can cause weakness and pain
- itching
- rash

- cough
- upset stomach or indigestion
- joint pain and back pain

Common side effects (affects 1 to 10 users in 100):

- allergic reactions including skin rashes (may be red, raised, itchy), severe swelling of the skin and other tissues
- inability to sleep (insomnia)
- anxiety
- increase in cholesterol
- increase in triglycerides
- gout
- stomach bleeding
- inflammation of the liver and yellowing of skin or whites of the eyes
- increase in urination
- reduced kidney function
- seizures (fits)
- low levels of blood platelets
- thirst (dehydration)
- abnormally heavy periods
- wind (flatulence)
- loss of appetite
- mouth ulcer
- muscle aches (pain), tenderness or weakness
- fever
- weight loss
- laboratory test results: changes in blood test results (such as blood chemistry and blood count)
- confusion
- difficulty paying attention
- fainting
- blurred vision
- swelling of the hands and feet
- high blood pressure
- low blood pressure and feeling faint when getting up
- coldness in the hands and feet
- acne

Uncommon side effects (affects 1 to 10 users in 1,000):

- heart attack
- diabetes
- kidney failure

Rare side effects (affects 1 to 10 users in 10,000):

- severe or life threatening skin reaction including blisters (Stevens Johnson syndrome, toxic epidermal necrolysis)
- serious allergic reaction (anaphylaxis)
- high levels of sugar in the blood

Tell your doctor if you feel sick (nauseous), are vomiting, or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your doctor if you experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. See also section **2 Before you take Norvir**.

In patients with haemophilia types A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Abnormal liver function tests, hepatitis (inflammation of the liver), and rarely jaundice, have been reported in patients taking Norvir. Some people had other illnesses or were taking other medicines. People with liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly when taking medicines to lower cholesterol in combination with antiretroviral therapy, including protease inhibitors and

nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis). In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop taking the medicine, contact your doctor as soon as possible or go to the Accident and Emergency Department of your nearest hospital.

Inform your doctor as soon as possible if you experience any symptoms that suggest an allergic reaction after taking Norvir such as rash, hives or breathing difficulties.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, contact your doctor, pharmacist, Accident and Emergency department or if it is urgent get immediate medical help.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Norvir

Keep this medicine out of the sight and reach of children.

Do not use Norvir powder for oral suspension after the expiry date on the sachet and carton. The expiry date refers to the last day of the month.

Norvir powder for oral suspension should be stored below 30°C.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Norvir contains

- The active substance is ritonavir. Each sachet of Norvir contains 100 mg ritonavir.
- The other ingredients are copovidone; sorbitan laurate; silica, colloidal anhydrous.

What Norvir looks like and contents of the pack

Norvir powder for oral suspension comes in individual sachets containing 100 mg ritonavir. 30 sachets are packed in a carton together with 1 mixing cup and 2 oral dosing syringes.

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Package leaflet: Information for the user

Norvir 100 mg film-coated tablets ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4..

What is in this leaflet:

1. What Norvir is and what it is used for
2. What you need to know before you take Norvir
3. How to take Norvir
4. Possible side effects
5. How to store Norvir
6. Contents of the pack and other information

1. What Norvir is and what it is used for

Norvir contains the active substance ritonavir. Norvir is a protease inhibitor used to control HIV infection. Norvir is used in combination with other anti-HIV medicines (antiretrovirals) to control your HIV infection.

Norvir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS. Norvir should not be administered to children younger than 2 years of age unless specifically directed by their doctor.

Norvir can be used at full dose on its own, or at lower doses (called booster doses) with other medicines. Your doctor will discuss with you the best combination of medicines for you.

2. What you need to know before you take Norvir

Do not take Norvir

- if you are allergic to ritonavir or any of the other ingredients of Norvir (see section 6).
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
 - amiodarone, bepridil, encainide, flecainide, propafenone, quinidine (used to correct irregular heartbeats);
 - dihydroergotamine, ergotamine (used to treat migraine headache);
 - ergonovine, methylegonovine (used to stop excessive bleeding that may occur following childbirth or an abortion);

- clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety);
- clozapine, pimozide, (used to treat abnormal thoughts or feelings);
- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
- pethidine, piroxicam, propoxyphene (used to relieve pain);
- cisapride (used to relieve certain stomach problems);
- rifabutin (used to prevent/treat certain infections)*;
- voriconazole (used to treat fungal infections)*;
- simvastatin, lovastatin (used to lower blood cholesterol);
- alfuzosin (used to treat enlarged prostate gland);
- fusidic acid (used to treat bacterial infections);
- sildenafil if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without this disease may use sildenafil for impotence (erectile dysfunction) under their doctor’s supervision (see the section on **Other medicines and Norvir**);
- avanafil or vardenafil (used to treat erectile dysfunction);
- products containing St John’s wort (*Hypericum perforatum*) as this may stop Norvir from working properly. St John’s wort is often used in herbal medicines that you can buy yourself.

* Your doctor may decide that you can take rifabutin and/or voriconazole with a booster (lower dose) of Norvir but a full dose of Norvir must not be taken together with these two medicines.

If you are currently taking any of these medicines, ask your doctor about switching to a different medicine while you are taking Norvir. Often, there are other medicines you can take instead.

Also read the list of medicines under ‘Other medicines and Norvir’ for use with certain other medicines which require special care.

Warnings and precautions

Talk to your doctor before taking Norvir.

Important information

- If Norvir is taken in combination with other antiretroviral medicines, it is important that you also carefully read the leaflets that are provided with these other medicines. There may be additional information in those leaflets about situations when Norvir should be avoided. If you have any further questions about Norvir (ritonavir) or the other medicines prescribed, please ask your doctor or pharmacist.
- Norvir is not a cure for HIV infection or AIDS.
- People taking Norvir may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of your doctor while taking Norvir.
- You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

Tell your doctor if you have/had:

- A history of **liver disease**.
- **Hepatitis B or C** and are being treated with a combination of antiretroviral agents, as you are at a greater risk of a severe and potentially life threatening reaction because of the effect on the liver. Regular blood tests may be required to check your liver is working properly.

- **Haemophilia**, as there have been reports of increased bleeding in patients with haemophilia who are taking this type of medicine (protease inhibitors). The reason for this is not known. You may need additional medicine to help your blood clot (factor VIII), in order to control any bleeding.
- **Erectile Dysfunction**, as the medicines used to treat erectile dysfunction can cause hypotension and prolonged erection.
- **Diabetes**, as there have been reports of worsening of or the development of diabetes (diabetes mellitus) in some patients taking protease inhibitors.
- **Kidney (renal) disease**, since your doctor may need to check the dose of your other medicines (such as protease inhibitors).

Tell your doctor if you experience:

- **Diarrhoea or vomiting** that is not improving (persistent), as this may reduce how well the medicines you are taking work.
- **Feeling sick** (nausea), **vomiting** or have **stomach pain**, because these may be signs of inflammation of the pancreas (pancreatitis). Some patients taking Norvir can develop serious problems with their pancreas. Tell your doctor as soon as possible if this applies to you.
- **Symptoms of infection** – inform your doctor immediately. Some patients with advanced HIV infection (AIDS) who then start anti-HIV treatment may develop the symptoms of infections they have had in the past even if they didn't know they had had them. It is believed that this happens because the body's immune response improves and helps the body to fight these infections.
In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty moving, tell your doctor, as this may be a sign of a problem that can destroy bone (osteonecrosis). Some patients taking a number of antiretroviral medicines may develop this disease.
- **Muscle pain, tenderness or weakness**, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious. (See section 4 **Possible side effects**)
- **Dizziness, lightheadedness, fainting spells or abnormal heartbeat**. Some patients taking Norvir may experience changes in the electrocardiogram (ECG). Tell your doctor if you have a heart defect or conduction defect.
- If you have any other health concerns, discuss these with your doctor as soon as you can.

Norvir is not recommended in children below 2 years of age.

Other medicines and Norvir

There are some medicines you cannot take at all with Norvir. These are listed earlier in Section 2, under 'Do not take Norvir'. There are some other medicines that can only be used under certain circumstances as described below. Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

The following warnings apply when Norvir is taken as a full dose. However, these warnings may also apply when Norvir is used in lower doses (a booster) with other medicines.

Tell your doctor if you are taking any of the medicines listed below, as special care should be taken.

- **Sildenafil or tadalafil** for impotence (erectile dysfunction).
The dose and/or frequency of use of these medicines may need to be reduced to avoid hypotension and prolonged erection. You must not take Norvir with sildenafil if you suffer from pulmonary arterial hypertension (see also section 2. **Before you take Norvir**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.
- **Digoxin** (heart medicine). Your doctor may need to adjust the dose of digoxin and monitor you while you are taking digoxin and Norvir in order to avoid heart problems.
- **Hormonal contraceptives** containing ethinyl oestradiol as Norvir may reduce the effectiveness of these medicines. It is recommended that a condom or other non-hormonal method of contraception is used instead. You may also notice irregular uterine bleeding if you are taking this type of hormonal contraceptive with Norvir.
- **Atorvastatin or rosuvastatin** (for high cholesterol) as Norvir may raise the blood levels of these medicines. Talk to your doctor before you take any cholesterol-reducing medicines with Norvir (see also ‘**Do not take Norvir**’ above).
- **Steroids** (e.g. dexamethasone, fluticasone propionate, prednisolone) as Norvir may raise the blood levels of these medicines which may lead to Cushing’s syndrome (development of a rounded face) and reduce production of the hormone cortisol. Your doctor may wish to reduce the steroid dose or monitor your side effects more closely.
- **Trazodone** (a medicine for depression) as, unwanted effects like nausea, dizziness, low blood pressure and fainting can occur when taken with Norvir.
- **Rifampicin and saquinavir** (used for tuberculosis and HIV, respectively) as serious liver damage can occur when taken with Norvir.
- **Bosentan** (used for pulmonary arterial hypertension) as Norvir may increase the blood levels of this medicine.

There are medicines that may not mix with Norvir because their effects could increase or decrease when taken together. In some cases your doctor may need to perform certain tests, change the dose or monitor you regularly. This is why you should tell your doctor if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention these:

- amphetamine or amphetamine derivatives;
- antibiotics (e.g. erythromycin, clarithromycin);
- anticancer treatments (e.g. dasatinib, nilotinib, vincristine, vinblastine);
- anticoagulants (e.g. rivaroxaban, warfarin);
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole);
- antihistamines (e.g. loratidine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors and Non-nucleoside reverse transcriptase inhibitors(NNRTI);
- anti-tuberculosis medicine (bedaquiline);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (simeprevir);
- anxiety medicine, buspirone;
- asthma medicine, theophylline, salmeterol;
- atovaquone, a medicine used to treat a certain type of pneumonia and malaria;
- buprenorphine, a medicine used for the treatment of chronic pain;
- bupropion, a medicine used to help you stop smoking;
- epilepsy medicines (e.g. carbamazepine, divalproex, lamotrigine, phenytoin);

- heart medicines (e.g. digoxin, disopyramide, mexiletine and calcium channel antagonists such as amlodipine, diltiazem and nifedipine);
- immune system (e.g. cyclosporine, tacrolimus, everolimus);
- morphine and morphine-like medicines used to treat severe pain (e.g. methadone, fentanyl);
- sleeping pills (e.g. alprazolam, zolpidem) and also midazolam administered by injection;
- tranquillisers (e.g. haloperidol, risperidone, thioridazine);
- Colchicine, a treatment for gout.

There are some medicines you cannot take at all with Norvir. These are listed earlier in section 2, under ‘Do not take Norvir’.

Taking Norvir with food and drink

Norvir tablets should be taken with food.

Pregnancy and breast-feeding

If you think you are pregnant or you are planning to become pregnant, it is very important that you discuss this with your doctor.

There is very little information on the use of ritonavir (the active ingredient in Norvir) during pregnancy. In general, the pregnant mothers received ritonavir after the first three months of pregnancy at a lower dose (booster) along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

It is not known if Norvir passes into breast milk. To avoid transmitting the infection, mothers with HIV should not breast feed their babies.

Driving and using machines

Norvir can cause sleepiness and dizziness. If you are affected do not drive or use machinery.

3. How to take Norvir

Always take Norvir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. It is taken by mouth usually two times every day. Norvir tablets should be taken with food as this can affect the way in which Norvir is absorbed into your body.

It is important that Norvir tablets are swallowed whole and not chewed, broken or crushed.

Recommended doses of Norvir are:

- if Norvir is used to boost the effects of certain other anti-HIV medicines the typical dose for adults is 1 to 2 tablets once or twice daily. For more detailed dose recommendations, including those for children, see the Package Leaflet of the anti-HIV medicines Norvir is given in combination with.
- if your doctor prescribes a full dose, adults may be started on a dose of 3 tablets in the morning and 3 tablets 12 hours later, gradually increasing over a period of up to 14 days to the full dose of 6 tablets twice daily (totaling 1,200mg per day). Children (2 – 12 years of age) will start with a dose smaller than this and continue up to the maximum allowed for their size.

Your doctor will advise you on the dosage to be taken.

Like all anti-HIV medicines, Norvir should be taken every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking Norvir as directed, tell your doctor straight away. During episodes of diarrhoea your doctor may decide that extra monitoring is needed.

Always keep enough Norvir on hand so you don't run out. When you travel or need to stay in the hospital, make sure you have enough Norvir to last until you can get a new supply.

If you take more Norvir than you should

Numbness, tingling, or a “pins and needles” sensation may occur if you take too much Norvir. If you realise you have taken more Norvir than you were supposed to, contact your doctor or the Accident and Emergency Department of your nearest hospital straight away.

If you forget to take Norvir

If you miss a dose, take the missed dose as soon as possible. If it is nearly time for the next dose, just take that one. Do not take a double dose to make up for a forgotten dose.

If you stop taking Norvir

Even if you feel better, do not stop taking Norvir without talking to your doctor. Taking Norvir as recommended should give you the best chance of delaying resistance to the medicines.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, Norvir can cause side effects, although not everybody gets them. Also, the side effects of Norvir when used with other antiretroviral medicines are dependent on the other medicines. So it is important that you carefully read the side effects section of the leaflets that are provided with these other medicines.

The frequency of possible side effects listed below is defined using the following convention:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data.

Very common side effects:

- upper or lower stomach ache
- vomiting
- diarrhoea (may be severe)
- feeling sick (nausea)
- headache
- flushing, feeling hot
- dizziness
- pain in the throat
- a tingling sensation or numbness in the hands, feet or around the lips and mouth
- feeling weak/tired
- bad taste in the mouth
- damage to the nerves that can cause weakness and pain
- itching

- cough
- upset stomach or indigestion
- rash
- joint pain and back pain

Common side effects:

- allergic reactions including skin rashes (may be red, raised, itchy), severe swelling of the skin and other tissues
- inability to sleep (insomnia)
- anxiety
- increase in cholesterol
- increase in triglycerides
- gout
- stomach bleeding
- inflammation of the liver and yellowing of skin or whites of the eyes
- increase in urination
- reduced kidney function
- low levels of blood platelets
- seizures (fits)
- thirst (dehydration)
- abnormally heavy periods
- wind (flatulence)
- loss of appetite
- mouth ulcer
- muscle aches (pain), tenderness or weakness
- fever
- weight loss
- laboratory test results: changes in blood test results (such as blood chemistry and blood count)
- confusion
- difficulty paying attention
- fainting
- blurred vision
- swelling of the hands and feet
- high blood pressure
- low blood pressure and feeling faint when getting up
- coldness in the hands and feet
- acne

Uncommon side effects:

- heart attack
- diabetes
- kidney failure

Rare side effects:

- severe or life threatening skin reaction including blisters (Stevens Johnson syndrome, toxic epidermal necrolysis)
- serious allergic reaction (anaphylaxis)
- high levels of sugar in the blood

Tell your doctor if you feel sick (nauseous), are vomiting, or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your doctor if you experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. See also section 2 **Before you take Norvir**.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your doctor.

Abnormal liver function tests, hepatitis (inflammation of the liver), and rarely jaundice, have been reported in patients taking Norvir. Some people had other illnesses or were taking other medicines. People with liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly when taking medicines to lower cholesterol in combination with antiretroviral therapy, including protease inhibitors and

nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis). In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop taking the medicine, contact your doctor as soon as possible or go to the Accident and Emergency Department of your nearest hospital.

Inform your doctor as soon as possible if you experience any symptoms that suggest an allergic reaction after taking Norvir such as rash, hives or breathing difficulties.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, contact your doctor, pharmacist, Accident and Emergency department or if it is urgent get immediate medical help.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Norvir

Keep this medicine out of the sight and reach of children.

Do not use Norvir after the expiry date on the label. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original bottle in order to protect from moisture.

6. Contents of the pack and other information

What Norvir contains

- The active substance is ritonavir. Each film-coated tablet contains 100 mg ritonavir.
- The other tablet ingredients are: copovidone, sorbitan laurate, anhydrous calcium hydrogen phosphate, colloidal anhydrous silica, sodium stearyl fumarate.
- The tablet coating is composed of: hypromellose, titanium dioxide, macrogols, hydroxypropyl cellulose, talc, colloidal anhydrous silica, polysorbate 80.

What Norvir looks like and contents of the pack

Norvir film-coated tablets are white debossed with [Abbott logo] and the code “NK”.

Three pack sizes are available for Norvir tablets:

- 1 bottle of 30 tablets
- 1 bottle of 60 tablets
- Multipacks comprising 3 bottles each containing 30 film-coated tablets (90 tablets)

Not all pack sizes may be marketed.

Norvir is also supplied as an oral solution containing 80 mg/ml of ritonavir and a soft gel capsule containing 100 mg ritonavir.

Marketing Authorisation Holder

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Manufacturers

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>