ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.

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 as a pharmacokinetic enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected patients (adults and children of 2 years of age and older) (see sections 4.2, 4.4, 5.1, 5.2).

4.2 Posology and method of administration

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

Posology

When ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors the Summary of Product Characteristics (SmPC) 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

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.
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 SmPC of other protease inhibitors approved for co-administration with ritonavir.

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 for ritonavir is necessary for elderly patients (see section 5.2).

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, a decrease in the total body clearance of ritonavir is not expected in patients with renal impairment.

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 protease inhibitor may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. The SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information in this patient population.

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.

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

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. The enzyme-modulating effect of ritonavir may be dose dependent (see section 5.1). 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:

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, propoxyphene	Increased plasma concentrations of norpethidine and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity (see section 4.5).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose-titration phase (see section 4.5).
Antiarrhythmics	Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, 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.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
	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.
Lipid-modifying agents		
HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (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 co-administration 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 (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

General

Ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors. Full details on the warnings and precautions relevant to that particular protease inhibitor should be considered, therefore the SmPC for the particular protease inhibitor must be consulted.

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. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients with coexisting conditions

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 Reconstitution Inflammatory 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 and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; 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, a decrease in the total body clearance of ritonavir 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 (DF) in clinical practice (see section 4.8).

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

Interactions with other medicinal products

HIV-protease inhibitors co-administered with ritonavir

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 protease inhibitors, see section 4.5. Please also review the SmPC for the particular boosted protease inhibitor.

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 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted. Refer to the SmPC for atazanavir for further details.

Other non-antiretroviral medicinal products co-administered with Ritonavir

The following warnings and precautions should be considered if 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 protease inhibitor must be considered, therefore the SmPC, section 4.4, for the particular protease inhibitor 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).

Colchicine
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see sections 4.3 and 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 oestradiol
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 oestradiol-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).

Riociguat
The concomitant use of ritonavir is not recommended due to potential increase in riociguat exposure (see section 4.5).

Vorapaxar
The concomitant use of ritonavir is not recommended due to potential increase in vorapaxar exposure (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 SmPC).

Delamanid
Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.5 and refer to the delamanid SmPC).

Medication error

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

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For 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 (e.g. digoxin and fexofenadine-see table "Ritonavir effects on non-antiretroviral medicinal products" below). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect.

Important information regarding medicinal product interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the SmPC 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. 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. This list is not intended to be inclusive or comprehensive. Individual SmPCs should be consulted.

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}
Atazanavir	300 q24h	100 q24h	Atazanavir	↑ 86%	↑ 11 fold
			Atazanavir[1]	↑ 2 fold	↑ 3-7 fold
	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the SmPC 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 SmPC 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 SmPC for fosamprenavir.				
Indinavir	800 q12h	100 q12h	Indinavir[2]	↑ 178%	ND
			Ritonavir	↑ 72%	ND
	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
	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.				
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 SmPC for tipranavir.				

ND: Not determined.

1. Based on cross-study comparison to 400 mg atazanavir once daily alone.
2. Based on cross-study comparison to 800 mg indinavir 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}**
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 SmPC for maraviroc.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-adminsitration of ritonavir and raltegravir results in a minor reduction in raltegravir levels				

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}
Alpha$_1$-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of norpethidine and propoxyphene and is therefore **contraindicated** (see section 4.3).			
Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (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.			

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}
Antianginal				
Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).			
Antiarrthymics				
Amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, and quinidine and is therefore **contraindicated** (see section 4.3).			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND
	0.4 single oral dose	200 q12h, 13 days	↑ 22%	↔
	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 and kinase inhibitors				
Afatinib	20 mg, single dose	200 q12h/1h before	↑ 48%	↑ 39%
	40 mg, single dose			
	40 mg, single dose	200 q12h/ co-administered	↑ 19%	↑ 4%
		200 q12h/6h after	↑ 11%	↑ 5%
	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with ritonavir (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.			
Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and ritonavir should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.			

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}
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of ritonavir and potential loss of virologic response. In addition, serum concentrations may be increased when co-administered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of ritonavir with apalutamide is not recommended.			
Ceritinib	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with ritonavir. Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.			
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.			
Encorafenib	Serum concentrations may be increased when co-administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.			
Fostamatinib	Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib SmPC for dose reduction recommendations if such events occur.			
Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome. Co-administration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.			
Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with ritonavir is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).			
Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (see section 4.3 and refer to the venetoclax SmPC). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).			

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}
Anticoagulants				
Dabigatran etexilate Edoxaban	Serum concentrations may be increased due to P-gp inhibition by ritonavir. Clinical monitoring and/or dose reduction of the direct oral anticoagulants (DOAC) should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with ritonavir.			
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.			
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with ritonavir is not recommended (see section 4.4 and refer to the vorapaxar SmPC).			
Warfarin	5, single dose	400 q12h		
S-Warfarin			↑ 9%	↓ 9%
R-Warfarin			↓ 33%	↔
	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S- warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Anticonvulsants				
Carbamazepine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of carbamazepine. Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with ritonavir.			
Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.			

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of 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 co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition) in patients with renal and/or hepatic impairment (see sections 4.3 and 4.4). Refer to the colchicine SmPC.			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore **contraindicated** (see section 4.3).			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with ritonavir.			

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-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated** (see section 4.3).			
Rifabutin[1]	150 daily	500 q12h	↑ 4-fold	↑ 2.5-fold
25-*O*-desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	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 SmPC 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	100 q12h	↓ 39%	↓ 24%
	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 SmPC).			
Clarithromycin	500 q12h	200 q8h	↑ 77%	↑ 31%
14-OH clarithromycin metabolite			↓ 100%	↓ 99%

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}
	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%.			
Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid SmPC).			
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).			
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.			
Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone 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}
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of ritonavir 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 (Cmax) and area under the curve (AUC)			
Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with ritonavir is not recommended (see section 4.4 and refer to riociguat SmPC).			
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 Direct Acting Antiviral				
Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.			
HCV Protease Inhibitor				

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}
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 oestradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32%
	Due to reductions in ethinyl oestradiol 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 oestradiol-containing contraceptives (see section 4.4).			
Immunosupressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Lipid-modifying agents				
Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of ritonavir with lomitapide is contraindicated (see the SmPC for lomitapide) (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}
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).			
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
	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). When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC.			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
	Concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).			
Sedatives/hynoptics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			

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}
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore **contraindicated** (see section 4.3).			
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
	The use of pethidine and ritonavir is **contraindicated** due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures), see section 4.3.			
Alprazolam	1, single dose	200 q12h, 2 days	↑ 2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150	100 q12h	↓ 22%	↓ 21%
	150	600 q12h	↓ 66%	↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.			

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}
Steroids				
Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	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 and triamcinolone. 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.			
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.			
Thyroid hormone replacement therapy				
Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.			
	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 nefazodone. 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.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount (6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births 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 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). Norvir can be used during pregnancy if clinically needed.

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

Breast-feeding
Limited published data reports that ritonavir is present in human milk.

There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, women living with HIV should not breast-feed their infants if they are receiving Norvir.

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

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

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 (≥ 1/1 000 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
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

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
	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)
Musculosketal 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
	Not known	Nephrolithiasis
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 and autoimmune hepatitis) 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 population

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

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

achieved most commonly with ritonavir doses of 100 mg to 200 mg daily, and is dependent on the co-administered protease inhibitor.

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.

For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism, see section 4.5 and refer to the SmPC of the particular co-administered protease inhibitors.

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 SmPC 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

Ritonavir was initially developed and approved with a maximal daily dose of 1 200 mg daily as a standalone antiretroviral agent. Current treatment guidelines recommend use of ritonavir as a pharmacokinetic enhancer of other protease inhibitors at lower daily doses, and is most commonly used at doses of 100 to 200 mg/day. The SmPCs of the co-administered protease inhibitors describe the clinical development for ritonavir's use as a pharmacokinetic enhancer.

Paediatric population

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 naive and naive to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. In intent to treat analyses, 50% and 57% of patients in the 350 and 450 mg/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 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
C_{max} (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3
C_{trough} (µg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2
$AUC_{12 \text{ or } 24}$ (µg•h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48
$t_{½}$ (h)	~5	~5	~4	~8
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2

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

The pharmacokinetic interaction between ritonavir and indinavir was evaluated in 5 groups of healthy adult volunteers in a randomised, multiple-dose, open-label study. At steady state, ritonavir increased plasma indinavir concentrations with area under the curve (AUC) increased up to 475% and maximum concentration (C_{max}) increased up to 110%.

In a study to evaluate the pharmacokinetic interaction between ritonavir and saquinavir in healthy volunteers in 6 groups of a single-dose crossover study, co-administration of ritonavir and saquinavir resulted in a > 50-fold increase in the AUC and a 22-fold increase in the C_{max} of saquinavir.

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.

Biotransformation
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 of ritonavir are expected in patients with renal impairment.

Paediatric patients
Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children above 2 years of age receiving doses ranging from 250 mg/m^2 twice daily to 400 mg/m^2 twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice daily. Across dose groups,

ritonavir oral clearance (CL/F/m^2) was approximately 1.5 to 1.7 times faster in paediatric patients above 2 years of age than in adult subjects.

Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2) declined with age with median values of 9.0 L/h/m^2 in children less than 3 months of age, 7.8 L/h/m^2 in children between 3 and 6 months of age and 4.4 L/h/m^2 in children between 6 and 24 months of age.

5.3 Preclinical safety data

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea 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 (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone
Sorbitan laurate
Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 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 washed in warm water and dish soap, then rinsed and allowed to air dry prior to first 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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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

Detailed information on this product is available on the website of the European Medicines Agency https://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 “NK” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ritonavir is indicated as a pharmacokinetic enhancer of co-administered protease inhibitors as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected patients (adults and children of 2 years of age and older) (see sections 4.2, 4.4, 5.1, 5.2).

4.2 Posology and method of administration

Ritonavir should be prescribed 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.

Posology

When ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors the Summary of Product Characteristics (SmPC) 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

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.
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 SmPC of other protease inhibitors approved for co-administration with ritonavir.

Special populations

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

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, a decrease in the total body clearance of ritonavir is not expected in patients with renal impairment.

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 protease inhibitor may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. The SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information in this patient population.

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.

4.3 Contraindications

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

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

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. The enzyme-modulating effect of ritonavir may be dose dependent (see section 5.1). 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:

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, propoxyphene	Increased plasma concentrations of norpethidine and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity (see section 4.5).
	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose-titration phase (see section 4.5).
Antiarrhythmics	Amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, 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.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
	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.
Lipid-modifying agents		

HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
Microsomal triglyceride transfer protein (MTTP) inhibitor	Lomitapide	Increased plasma concentrations of lomitapide (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 co-administration 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 (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

General

Ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors. Full details on the warnings and precautions relevant to that particular protease inhibitor should be considered, therefore the SmPC for the particular protease inhibitor must be consulted.

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. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients with co-existing conditions

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 Reconstitution Inflammatory 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 and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; 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, a decrease in the total body clearance of ritonavir 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 (DF) in clinical practice (see section 4.8).

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

Interactions with other medicinal products

HIV-protease inhibitors co-administered with Ritonavir

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 protease inhibitors, see section 4.5. Please also review the SmPC for the particular boosted protease inhibitor.

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 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted. Refer to the SmPC for atazanavir for further details.

Other non-antiretroviral medicinal products co-administered with ritonavir

The following warnings and precautions should be considered if 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 protease inhibitor must be considered, therefore the SmPC, section 4.4, for the particular protease inhibitor 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).

Colchicine
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see sections 4.3 and 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 oestradiol
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 oestradiol-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).

Riociguat
The concomitant use of ritonavir is not recommended due to potential increase in riociguat exposure (see section 4.5).

Vorapaxar
The concomitant use of ritonavir is not recommended due to potential increase in vorapaxar exposure (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 SmPC).

Delamanid
Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.5 and refer to the delamanid SmPC).

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For 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 (e.g. digoxin and fexofenadine-see table "Ritonavir effects on non-antiretroviral medicinal products" below). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect.

Important information regarding medicinal product interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the SmPC 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. 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. This list is not intended to be inclusive or comprehensive. Individual SmPCs should be consulted.

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}
Atazanavir	300 q24h	100 q24h	Atazanavir	↑ 86%	↑ 11 fold
			Atazanavir[1]	↑ 2 fold	↑ 3-7 fold
	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the SmPC 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 SmPC 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 SmPC for fosamprenavir.				
Indinavir	800 q12h	100 q12h	Indinavir[2]	↑ 178%	ND
			Ritonavir	↑ 72%	ND
	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
	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.				
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 SmPC for tipranavir.				

ND: Not determined.

1. Based on cross-study comparison to 400 mg atazanavir once daily alone.
2. Based on cross-study comparison to 800 mg indinavir 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}
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 SmPC for maraviroc.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-adminsitration of ritonavir and raltegravir results in a minor reduction in raltegravir levels				

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}
Alpha$_1$-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SmPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of norpethidine 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.			
Antianginal				
Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).			
Antiarrthymics				
Amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, and quinidine and is therefore **contraindicated** (see section 4.3).			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND
	0.4 single oral dose	200 q12h, 13 days	↑ 22%	↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antriretroviral agent or as a pharmacokinetic enhancer. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops (see section 4.4).			
Antiasthmatic				
Theophylline[1]	3 mg/kg q8h	500 q12h	↓ 43%	↓ 32%
	An increased dose of theophyline may be required when co-administered with ritonavir, due to induction of CYP1A2.			
Anticancer agents and kinase inhibitors				
Afatinib	20 mg, single dose 40 mg, single dose 40 mg, single dose	200 q12h/1h before	↑ 48% ↑ 19%	↑ 39% ↑ 4%

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}
		200 q12h/ co-administered 200 q12h/6h after	↑ 11%	↑ 5%
	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with ritonavir (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.			
Abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and ritonavir should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.			
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of ritonavir and potential loss of virologic response. In addition, serum concentrations may be increased when co-administered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of ritonavir with apalutamide is not recommended.			
Ceritinib	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with ritonavir. Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.			
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.			
Encorafenib	Serum concentrations may be increased when co-administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.			
Fostamatinib	Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib SmPC for dose reduction recommendations if such events occur.			

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}
Ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumor lysis syndrome. Co-administration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.			
Neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with ritonavir is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).			
Venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (see section 4.3 and refer to the venetoclax SmPC). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).			
Anticoagulants				
Dabigatran etexilate Edoxaban	Serum concentrations may be increased due to P-gp inhibition by ritonavir. Clinical monitoring and/or dose reduction of the direct oral anticoagulants (DOAC) should be considered when a DOAC transported by P-gp but not metabolised by CYP3A4, including dabigatran etexilate and edoxaban, is co-administered with ritonavir.			
Rivaroxaban	10, single dose 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.	600 q12h	↑ 153%	↑ 55%
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with ritonavir is not recommended (see section 4.4 and refer to the vorapaxar SmPC).			
Warfarin S-Warfarin R-Warfarin	5, single dose 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.	400 q12h	 ↑ 9% ↓ 33%	 ↓ 9% ↔

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}
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 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 co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition) in patients with renal and/or hepatic impairment (see sections 4.3 and 4.4). Refer to the colchicineSmPC.			
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).			

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}
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with ritonavir.			
Anti-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated** (see section 4.3).			
Rifabutin[1]	150 daily	500 q12h,	↑ 4-fold	↑ 2.5-fold
25-*O*-desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	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 SmPC 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	100 q12h	↓ 39%	↓ 24%
	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.			

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}
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 SmPC).			
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%.			
Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid SmPC).			
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.			

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}
Antipsychotics/Neuroleptics				
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore **contraindicated** (see section 4.3).			
Haloperidol, risperidone, thioridazine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.			
Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 4.3).			
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of ritonavir 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).			
Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with ritonavir is not recommended (see section 4.4 and refer to riociguat SmPC).			
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).			

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}
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 Direct Acting Antiviral				
Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.			
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, Pravstatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is **contraindicated** (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.			
Hormonal contraceptive				
Ethinyl oestradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32%
	Due to reductions in ethinyl oestradiol 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 oestradiol-containing contraceptives (see section 4.4).			

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}
Immunosupressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Lipid-modifying agents				
Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of ritonavir with lomitapide is contraindicated (see the SmPC for lomitapide) (see section 4.3).			
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 with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours (see also section 4.4). Concomitant use of sildenafil with ritonavir is **contraindicated** in pulmonary arterial hypertension patients (see section 4.3).			
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
	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). When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil SmPC.			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
	Concomitant use of vardenafil 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}
Sedatives/hypnotics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore **contraindicated** (see section 4.3).			
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
	The use of pethidine and ritonavir is **contraindicated** due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures), 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}
Alprazolam	1, single dose	200 q12h, 2 days	↑ 2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150	100 q12h	↓ 22%	↓ 21%
	150	600 q12h	↓ 66%	↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.			
Steroids				
Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	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 and triamcinolone. 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.,			

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}
	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.			
Thyroid hormone replacement therapy				
Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.			
	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 nefazodone. 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.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount (6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births 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 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). Norvir can be used during pregnancy if clinically needed.

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

Breast-feeding
Limited published data reports that ritonavir is present in human milk.

There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, women living with HIV should not breast-feed their infants if they are receiving Norvir.

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

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

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 (≥ 1/1 000 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 white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia
	Uncommon	Increased neutrophils
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)

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculosketal 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 Not known	Acute renal failure Nephrolithiasis
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

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 and autoimmune hepatitis) 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 population

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 1 500 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

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

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 achieved most commonly with ritonavir doses of 100 mg to 200 mg daily, and is dependent on the co-administered protease inhibitor.

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.

For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism, see section 4.5 and refer to the SmPC of the particular co-administered protease inhibitors.

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 SmPC 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

Ritonavir was initially developed and approved with a maximal daily dose of 1 200 mg daily as a standalone antiretroviral agent. Current treatment guidelines recommend use of ritonavir as a pharmacokinetic enhancer of other protease inhibitors at lower daily doses, and is most commonly used at doses of 100 to 200 mg/day. The SmPCs of the co-administered protease inhibitors describe the clinical development for ritonavir's use as a pharmacokinetic enhancer.

Paediatric population

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 naive and naive to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m^2 every 12 hours co-administered with lamivudine and stavudine. In intent to treat analyses, 50% and 57% of patients in the 350 and 450 mg/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. 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
C_{max} (μg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3
C_{trough} (μg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2
$AUC_{12 \text{ or } 24}$ (μg•h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48
$t_{½}$ (h)	~5	~5	~4	~8
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2

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

The pharmacokinetic interaction between ritonavir and indinavir was evaluated in 5 groups of healthy adult volunteers in a randomised, multiple-dose, open-label study. At steady state, ritonavir increased plasma indinavir concentrations with area under the curve (AUC) increased up to 475% and maximum concentration (C_{max}) increased up to 110%.

In a study to evaluate the pharmacokinetic interaction between ritonavir and saquinavir in healthy volunteers in 6 groups of a single-dose crossover study, co-administration of ritonavir and saquinavir resulted in a > 50-fold increase in the AUC and a 22-fold increase in the C_{max} of saquinavir.

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 ^{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.

Biotransformation
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 of ritonavir are expected in patients with renal impairment.

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

Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m² twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance (CL/F/m^2)

declined with age with median values of 9.0 L/h/m^2 in children less than 3 months of age, 7.8 L/h/m^2 in children between 3 and 6 months of age and 4.4 L/h/m^2 in children between 6 and 24 months of age.

5.3 Preclinical safety data

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea 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 (embryolethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

18 months

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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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

Detailed information on this product is available on the website of the European Medicines Agency https://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 manufacturers 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

or

AbbVie S.r.l., S.R. 148 Pontina km 52 SNC, 04011 Campoverde di Aprilia (LT), Italy

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 (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs 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 POWDER FOR ORAL SUSPENSION - Carton containing 30 sachets each containing 100 mg 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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Norvir 100 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/016/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

B. PACKAGE LEAFLET

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

Norvir contains the active substance ritonavir. Norvir is a protease inhibitor used in combination with other anti-HIV medicines (antiretrovirals) as a booster (pharmacokinetic enhancer) to control your HIV infection. Norvir as an enhancer does not directly treat your HIV, but boosts the levels of other protease inhibitors in the blood to improve their effect 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 takes 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, dronedarone, 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);

- lurasidone (used to treat depression);
- ranolazine (used to treat chronic chest pain [angina]);
- pethidine, propoxyphene (used to relieve pain);
- cisapride (used to relieve certain stomach problems);
- simvastatin, lovastatin (used to lower blood cholesterol);
- neratinib (used to treat breast cancer);
- lomitapide (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);
- colchicine (used to treat gout) if you have kidney and/or liver problems (see the section on **Other medicines and Norvir**);
- 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.

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.

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 may apply when Norvir is used as a booster (pharmacokinetic enhancer) 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. **What you need to know before you or your child takes Norvir**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.
- **Colchicine** (for gout) as Norvir may raise the blood levels of this medicine. You must not take Norvir with colchicine if you have kidney and/or liver problems (see also '**Do not take Norvir**' above).
- **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, triamcinolone) 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** (used for tuberculosis) as serious liver damage can occur when taken with Norvir.
- **Bosentan, riociguat** (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, rifabutin);
- anticancer treatments (e.g. abemaciclib, afatinib, apalutamide, ceritinib, encorafenib, dasatinib, ibrutinib, nilotinib, venetoclax, vincristine, vinblastine);
- medicines used to treat low blood platelet count (e.g. fostamatinib);
- anticoagulants (e.g. dabigatran etexilate, edoxaban, rivaroxaban, vorapaxar, warfarin);
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole, voriconazole);
- antihistamines (e.g. loratadine, fexofenadine);
- antiretroviral medicines, including HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, tipranavir), non-nucleoside reverse transcriptase inhibitors (NNRTI), and others (maraviroc, raltegravir);
- anti-tuberculosis medicine (bedaquiline and delamanid);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (e.g. glecaprevir/pibrentasvir and 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);
- levothyroxine (used to treat thyroid problems);
- 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 are pregnant, think you may be pregnant or are planning to have a baby, it is very important that you ask your doctor for advice before taking this medicine.

There is a large amount of 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 as a booster (pharmacokinetic enhancer) along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

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 or 200 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 dose of Norvir is:

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.

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:

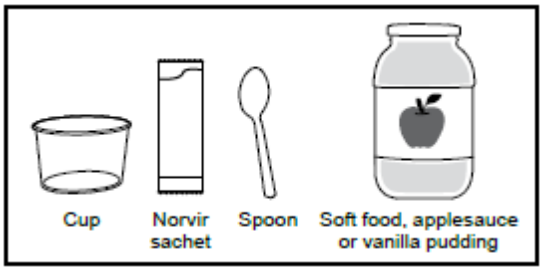


Figure 1

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.

Step 3. Before first using the mixing cup, wash the cup in warm water and dish soap. Rinse and allow to air dry.

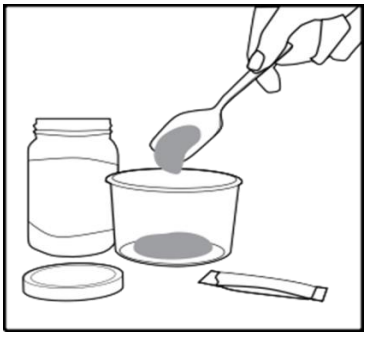
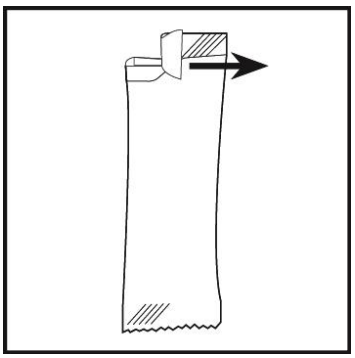


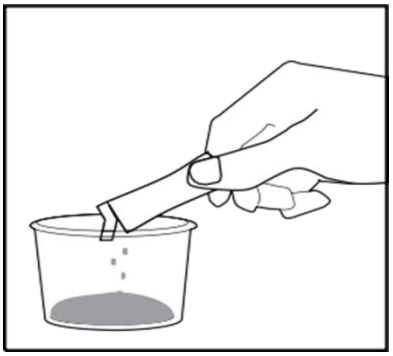
Figure 2

Step 4. Put a small serving of soft food (applesauce or vanilla pudding) in a cup (see Figure 2).



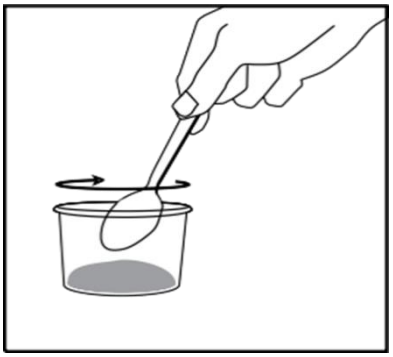
Step 5. Tear open sachet (see Figure 3).

Figure 3



Step 6. Pour ALL powder from sachet onto food (see Figure 4).

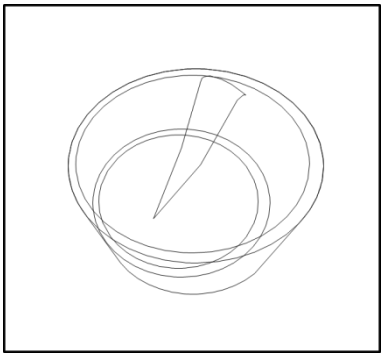
Figure 4



Step 7. Mix thoroughly (see Figure 5).

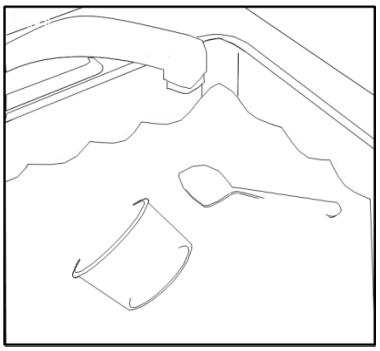
Figure 5

Step 8. Feed serving to patient.



Step 9. 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 6



Step 10. 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.

Figure 7

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

Follow the instructions below:

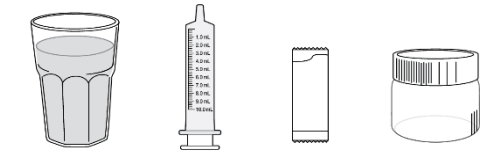
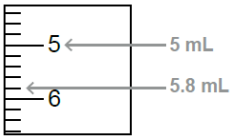


Figure 1

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
Before first using the dosing syringe, wash the syringe in warm water and dish soap. Rinse and allow to air dry.

Reading the scale

a. Each millilitre (ml) is shown as a number with a big line.
b. 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.

Figure 2

Step 1. Fill the syringe

a. Push the plunger all the way into syringe.
b. Place the syringe tip into the liquid.
c. Slowly pull the plunger back to the 10 ml mark on the syringe (see Figure 2).

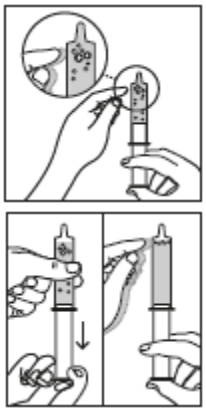


Figure 3

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).

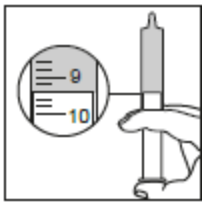


Figure 4

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).

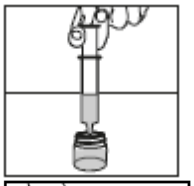


Figure 5

Step 4. Empty the syringe

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

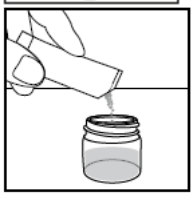


Figure 6

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).

Figure 7

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).

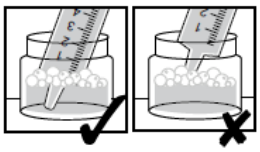


Figure 8

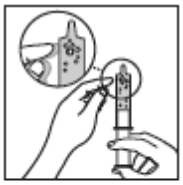


Figure 9

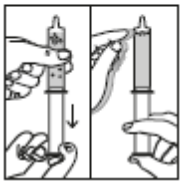


Figure 10

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: may affect more than 1 in 10 people

- upper or lower stomach ache
- vomiting
- diarrhoea (may be severe)
- feeling sick (nausea)
- flushing, feeling hot
- headache
- dizziness
- pain in the throat
- cough
- upset stomach or indigestion
- 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
- joint pain and back pain

Common: may affect up to 1 in 10 people

- 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: may affect up to 1 in 100 people

- heart attack
- diabetes
- kidney failure

Rare: may affect up to 1 in 1 000 people

- 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

Not known: frequency cannot be estimated from the available data

- kidney stones

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. What you need to know before you or your child takes 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 use this medicine if you notice the powder is not beige/pale yellow to yellow.

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.

Not all pack sizes may be marketed.

Norvir is also supplied as a film-coated tablet containing 100 mg ritonavir.

Marketing Authorisation Holder

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

Manufacturers

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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: https://www.ema.europa.eu

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

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 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. 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

Norvir contains the active substance ritonavir. Norvir is a protease inhibitor used in combination with other anti-HIV medicines (antiretrovirals) as a booster (pharmacokinetic enhancer) to control your HIV infection. Your doctor will discuss with you the best combination of medicines for you. Norvir as an enhancer does not directly treat your HIV, but boosts the levels of other protease inhibitors in the blood to improve their effect 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.

2. What you need to know before you or your child takes 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, dronedarone, 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);
- lurasidone (used to treat depression);
- ranolazine (used to treat chronic chest pain [angina]);
- pethidine, propoxyphene (used to relieve pain);
- cisapride (used to relieve certain stomach problems);
- simvastatin, lovastatin (used to lower blood cholesterol);
- neratinib (used to treat breast cancer);
- lomitapide (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);
- colchicine (used to treat gout) if you have kidney and/or liver problems (see the section on **Other medicines and Norvir**);
- 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.

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.

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 or 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 may apply when Norvir is used as a booster (pharmacokinetic enhancer) 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. **What you need to know before you or your child takes Norvir**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.

- **Colchicine** (for gout) as Norvir may raise the blood levels of this medicine. You must not take Norvir with colchicine if you have kidney and/or liver problems (see also '**Do not take Norvir**' above).
- **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, triamcinolone) 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** (used for tuberculosis) as serious liver damage can occur when taken with Norvir.
- **Bosentan, riociguat** (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, rifabutin);
- anticancer treatments (e.g. abemaciclib; afatinib, apalutamide, ceritinib, encorafenib, dasatinib, ibrutinib, nilotinib, venetoclax, vincristine, vinblastine);
- medicines used to treat low blood platelet count (e.g. fostamatinib);
- anticoagulants (e.g. dabigatran etexilate, edoxaban, rivaroxaban, vorapaxar, warfarin);
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole, voriconazole);
- antihistamines (e.g. loratidine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, tipranavir) non-nucleoside reverse transcriptase inhibitors (NNRTI) , and others (maraviroc, raltegravir);
- anti-tuberculosis medicine (bedaquiline and delamanid);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (e.g. glecaprevir/pibrentasvir and 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 (e.g. cyclosporine, tacrolimus, everolimus);
- levothyroxine (used to treat thyroid problems);
- 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 are pregnant, think you may be pregnant or are planning to have a baby, it is very important that you ask your doctor for advice before taking this medicine.

There is a large amount of 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 as a booster (pharmacokinetic enhancer) along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Driving and using machines

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

Norvir contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

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

Recommended dose of Norvir is:

Norvir is used to boost the effects of certain other anti-HIV medicines. The typical dose for adults is 1 or 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.

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 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.

Very common: may affect more than 1 in 10 people

- upper or lower stomach ache
- vomiting
- diarrhoea (may be severe)
- feeling sick (nausea)
- flushing, feeling hot
- headache
- dizziness
- pain in the throat
- cough
- upset stomach or indigestion
- 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
- joint pain and back pain

Common: may affect up to 1 in 10 people

- 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: may affect up to 1 in 100 people

- heart attack
- diabetes
- kidney failure

Rare: may affect up to 1 in 1 000 people

- 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

Not known: frequency cannot be estimated from the available data

- kidney stones

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. What you need to know before you or your child takes 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.

Do not use this medicine if you notice any discolouration.

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

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 the code “NK” on one side.

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 a powder for oral suspension containing 100 mg of ritonavir.

Marketing Authorisation Holder

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Manufacturers

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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: https://www.ema.europa.eu

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.