SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ritonavir Mylan 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of ritonavir.

Excipient with known effect
Each film-coated tablet contains 87.75 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow, capsule shaped, biconvex, beveled edge film-coated tablet, approximately 19.1 mm x 10.2 mm, debossed with ‘M163’ on one side and blank on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

Ritonavir dosed as a pharmacokinetic enhancer
When ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors the Summary of Product Characteristics for the particular protease inhibitor must be consulted.

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

Adults
Amprenavir 600 mg twice daily with ritonavir 100 mg twice daily.
Atazanavir 300 mg once daily with ritonavir 100 mg once daily.
Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily.
Lopinavir co-formulated with ritonavir (lopinavir/ritonavir) 400 mg/100 mg or 800 mg/200 mg.
Saquinavir 1,000 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients.
Initiate treatment with saquinavir 500 mg twice daily with ritonavir 100 mg twice daily for the first 7 days, then saquinavir 1,000 mg twice daily with ritonavir 100 mg twice daily in ART-naïve patients.
Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients.
Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in 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 Summary of Product Characteristics 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 dose recommendations, refer to the product information of other Protease Inhibitors approved for co-administration with ritonavir.

Special populations

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

Hepatic impairment
Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease, (see section 4.3). In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C)

without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur. Specific recommendations for use of ritonavir as a pharmacokinetic enhancer in patients with hepatic impairment are dependent on the protease inhibitor with which it is co-administered. The SPC of the co-administered PI should be reviewed for specific dosing information in this patient population.

Ritonavir dosed as an antiretroviral agent

Adults
The recommended dose of ritonavir is 600 mg (6 tablets) twice daily (total of 1,200 mg per day) by mouth.

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

Paediatric population (2 years of age and above)
The recommended dose of ritonavir in children is 350 mg/m^2 by mouth twice daily and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily.

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

For older children it may be feasible to substitute tablets for the maintenance dose of other pharmaceutical forms.

Table 1. Dose conversion from powder for oral suspension to tablets for children

Power for oral suspension dose	**Tablet dose**
175 mg (2.2 ml) twice daily	200 mg in the morning and 200 mg in the evening
350 mg (4.4 ml) twice daily	400 mg in the morning and 300 mg in the evening
437.5 mg (5.5 ml) twice daily	500 mg in the morning and 400 mg in the evening
525 mg (6.6 ml) twice daily	500 mg in the morning and 500 mg in the evening

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

Special populations

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

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

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

Paediatric population
The safety and efficacy of ritonavir 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

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

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

4.3 Contraindications

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

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

Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent to patients with decompensated liver disease.

In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. The following medicinal products 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 events.

The enzyme-modulating effect of ritonavir may be dose dependent. For some products, contraindications may be more relevant when ritonavir is used as an

antiretroviral agent than when ritonavir is used as a pharmacokinetic enhancer (e.g. rifabutin and voriconazole):

Table 2. Medicinal products that are contraindicated when used with Ritonavir

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.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect (see section 4.5).
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
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).
Antimycobacterial	Rifabutin	Concomitant use of ritonavir (500 mg twice daily) dosed as an antiretroviral agent and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse reactions including uveitis (see section 4.4). Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted in section 4.5.
Antipsychotics/ Neuroleptics	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 sections 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 sections 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

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.

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

Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer

Patients with chronic diarrhoea or malabsorption

Extra monitoring is recommended when diarrhoea occurs. The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medicinal products. Serious persistent vomiting and/or diarrhoea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment.

Haemophilia

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

Weight and metabolic parameters:

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

Pancreatitis

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir 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 asymtomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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, the decrease in the total body clearance is not expected in patients with renal impairment (see also section 4.2).

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate (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

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

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

HMG-CoA reductase inhibitors
The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolised to a lesser extent by CYP3A. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent of CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5).

Colchicine
Life-threatening and fatal 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.

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

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

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

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

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 Summary of Product Characteristics).

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 Summary of Product Characteristics).

Ritonavir dosed as a pharmacokinetic enhancer
The interaction profiles of HIV-protease inhibitors, co-administered with low dose ritonavir, are dependent on the specific co-administered protease inhibitor.

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

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

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

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

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

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

Atazanavir
Co-administration of atazanavir with ritonavir at doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended. Only when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. In this instance, close clinical monitoring is warranted. Refer to the Summary of Product Characteristics for atazanavir for further details.

Excipients
This medicinal product contains 87.75 mg sodium per tablet, equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The maximum daily dose of this product is equivalent to 53% of the WHO recommended maximum daily intake for sodium.

Ritonavir is considered high in sodium. This should be particularly taken into account for those on a low sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

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

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

Medicinal products that affect ritonavir levels

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

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

Medicinal 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.

Table 3. Medicinal product interactions – Ritonavir with protease inhibitors

Co-administered medicinal product	**Dose of co-administered medicinal product (mg)**	**Dose of ritonavir (mg)**	**Medicinal product assessed**	**AUC**	**C_{min}**
Amprenavir	600 q12 h	100 q12 h	Amprenavir[2]	↑ 64%	↑ 5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical studies confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. Ritonavir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations. For further information, physicians should refer to the Summary of Product Characteristics for amprenavir.				
Atazanavir	300 q24 h	100 q24 h	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 studies confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the Summary of Product Characteristics for atazanavir.				
Darunavir	600, single	100 q12 h	Darunavir	↑ 14 fold	
	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. Ritonavir doses higher than 100 mg twice daily have not been studied with darunavir. For further information, refer to the Summary of Product Characteristics for darunavir.				
Fosamprenavir	700 q12 h	100 q12 h	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 studies confirmed the safety and efficacy of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily. Ritonavir doses higher than 100 mg twice daily have not been studied with fosamprenavir. For further information, physicians should refer to the Summary of Product Characteristics for fosamprenavir.				
Indinavir	800 q12 h	100 q12 h	Indinavir[3]	↑ 178%	ND
			Ritonavir	↑ 72%	ND
	400 q12 h	400 q12 h	Indinavir[3]	↔	↑ 4 fold
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of indinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily. In cases of co-administration of ritonavir (100 mg twice daily) and indinavir (800 mg twice daily) caution is warranted as the risk of nephrolithiasis may be increased.				
Nelfinavir	1,250 q12 h	100 q12 h	Nelfinavir	↑ 20 to	ND

	750, single	500 q12 h	Nelfinavir Ritonavir	39% ↑ 152% ↔	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.				
Saquinavir	1,000 q12 h	100 q12 h	Saquinavir[4] Ritonavir	↑ 15-fold ↔	↑ 5-fold ↔
	400 q12 h	400 q12 h	Saquinavir[4] Ritonavir	↑ 17-fold ↔	ND ↔
	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir 100 mg twice daily with saquinavir 1,000 mg twice daily provides saquinavir systemic exposure over 24 hours similar to or greater than those achieved with saquinavir 1,200 mg three times daily without ritonavir. In a clinical study investigating the interaction of rifampicin 600 mg once daily and saquinavir 1,000 mg with ritonavir 100 mg twice daily in healthy volunteers, severe hepatocellular toxicity with transaminase elevations up to > 20-fold the upper limit of normal after 1 to 5 days of co-administration was noted. Due to the risk of severe hepatotoxicity, saquinavir/ritonavir should not be given together with rifampicin. For further information, physicians should refer to the Summary of Product Characteristics for saquinavir.				
Tipranavir	500 q12 h	200 q12 h	Tipranavir Ritonavir	↑ 11 fold ↓ 40%	↑ 29 fold ND
	Ritonavir increases the serum levels of tipranavir as a result of CYP3A inhibition. Tipranavir must be given with low dose ritonavir to ensure its therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used with tipranavir as they might alter the efficacy of the combination. For further information, physicians should refer to the Summary of Product Characteristics for tipranavir.				

ND: Not determined.
[1] Based on cross-study comparison to 400 mg atazanavir once daily alone.
[2] Based on cross-study comparison to 1,200 mg amprenavir twice daily alone.
[3] Based on cross-study comparison to 800 mg indinavir three times daily alone.
[4] Based on cross-study comparison to 600 mg saquinavir three times daily alone.

Table 4. Medicinal product interactions – Ritonavir with antiretroviral agents other than protease inhibitors

Co-administered medicinal product	**Dose of co-administered medicinal product (mg)**	**Dose of ritonavir (mg)**	**Medicinal product assessed**	**AUC**	**C_{min}**
Didanosine	200 q12 h	600 q12 h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on an empty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Delavirdine	400 q8 h	600 q12 h	Delavirdine[1] Ritonavir	↔ ↑ 50%	↔ ↑ 75%
	Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine,				

	dose reduction of ritonavir may be considered.				
Efavirenz	600 q24 h	500 q12 h	Efavirenz Ritonavir	↑ 21% ↑ 17%	
	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Maraviroc	100 q12 h	100 q12 h	Maraviroc	↑ 161%	↑ 28%
	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for maraviroc.				
Nevirapine	200 q12 h	600 q12 h	Nevirapine Ritonavir	↔ ↔	↔ ↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either nevirapine or ritonavir.				
Raltegravir	400 single	100 q12 h	Raltegravir	↓ 16%	↓ 1%
	Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.				
Zidovudine	200 q8 h	300 q6 h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.				
	ND: Not determined [1] Based on parallel group comparison.				

Table 5. Ritonavir effects on non-antiretroviral co-administered medicinal products

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
Alpha$_1$-Adrenoreceptor antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			
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 medicinal products are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24 h	100 q12 h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, 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 q12 h,	↓ 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			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	contraindicated (see section 4.3).			
Antiarrhythmics				
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 q12 h, 3 days	↑ 86%	ND
	0.4 single oral dose	200 q12 h, 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 q8 h	500 q12 h	↓ 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	200 q12 h/1 h before	↑ 48%	↑ 39%
	40 mg, single dose	200 q12 h/co-administered	↑ 19%	↑ 4%
	40 mg, single dose	200 q12 h/6 h 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 dose 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			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	administering ceritinib with ritonavir. Refer to the ceritinib SmPC for dose 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.			
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 tumour 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	600 q12 h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	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 q12 h		
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 medicinal products 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 medicinal products are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Desipramine	100, single oral dose	500 q12 h	↑ 145%	↑ 22%
	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15 and 67%, respectively. Dose reduction of desipramine is recommended when co-administered with ritonavir dosed as an antiretroviral agent.			
Trazodone	50, single dose	200 q12 h	↑ 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			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	with caution, initiating trazodone at the lowest dose 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 prescribing information.			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore **contraindicated** (see section 4.3).			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antiretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is concomitantly administered with ritonavir.			
Anti-infectives				
Fusidic acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated** (see section 4.3).			
Rifabutin[1]	150 daily	500 q12 h	↑ 4-fold	↑ 2.5-fold
25-*O*-desacetyl rifabutin metabolite			↑ 38-fold	↑ 16-fold
	Due to the large increase in rifabutin AUC, the concomitant use of rifabutin with ritonavir dosed as an antiretroviral agent is **contraindicated** (see section 4.3). The reduction of the rifabutin dose to 150 mg 3 times per week may be indicated for select PIs when co-administered with ritonavir as a pharmacokinetic enhancer. The Summary of Product Characteristics of the co-administered protease inhibitor should be consulted for specific recommendations. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV-infected patients.			
Rifampicin	Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administered with rifampicin, the additional inducing effect of rifampicin (next to that of ritonavir itself) is small and may have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The effect of ritonavir on rifampicin is not known.			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
Voriconazole	200 q12 h	400 q12 h	↓ 82%	↓ 66%
	200 q12 h	100 q12 h	↓ 39%	↓ 24%
	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole is **contraindicated** due to reduction in voriconazole concentrations (see section 4.3). Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.			
Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.			
Bedaquiline	No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline Summary of Product Characteristics).			
Clarithromycin	500 q12 h	200 q8 h	↑ 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 Summary of Product Characteristics)			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	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 q12 h	↑ 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 q12 h	↓ 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 medicinal products 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 medicinal products 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).			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
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				
Simeprevir	200 qd	100 q12 h	↑ 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				
Ethinylestradiol	50 µg, single dose	500 q12 h	↓ 40%	↓ 32%

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
	Due to reductions in ethinylestradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives (see section 4.4).			
Immunosuppressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicinal products 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 prescribing information for lomitapide) (see section 4.3).			
Phosphodiesterase (PDE5) inhibitors				
Avanafil	50, single dose	600 q12 h	↑ 13-fold	↑ 2.4-fold Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).
Sildenafil	100, single dose	500 q12 h	↑ 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 q12 h	↑ 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 Summary of Product Characteristics.
Vardenafil	5, single dose	600 q12 h	↑ 49-fold	↑ 13-fold Concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).
Sedatives/hypnotics				
Clorazepate, diazepam, estazolam,	Ritonavir co-administration is likely to result in increased plasma			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
flurazepam, oral and parenteral midazolam	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. Dose 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 q12 h	↓ 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 q12 h, 2 days	↑ 2.5 fold	↔
		500 q12 h, 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.			

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
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				
Buproprion	150	100 q12 h	↓ 22%	↓ 21%
	150	600 q12 h	↓ 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., 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 q12 h	↑ 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				

Co-administered medicinal products	Dose of co-administered medicinal products (mg)	Dose of ritonavir (mg)	Effect on co-administered medicinal products AUC	Effect on co-administered medicinal products C_{max}
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.

Ritonavir dosed as a pharmacokinetic enhancer

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

Proton pump inhibitors and 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 Summary of Product Characteristics 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). Ritonavir 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 ritonavir.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness is a known undesirable effect that should be taken into account when driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

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

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical studies 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, adverse reactions 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.

Table 6. 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)
Skin and subcutaneous tissue disorders	Very common	Pruritus, rash (including erythematous and maculopapular)
	Common	Acne
	Rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia and back pain
	Common	Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g. oliguria, elevated creatinine)
	Uncommon	Acute renal failure
	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 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 hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis (see section 4.4).

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

Paediatric populations
The safety profile of ritonavir 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 Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Human experience of acute overdose with ritonavir is limited. One patient in clinical studies 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 medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Ritonavir dosed as a pharmacokinetic enhancer

Pharmacokinetic enhancement by ritonavir is based on ritonavir's activity as a potent inhibitor of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co-administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Maximal inhibition of metabolism of the co-administered protease inhibitor is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily, and is dependent on the co-administered protease inhibitor. For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism, see section 4.5 and refer to the Summary of Product Characteristics of the particular co-administered PIs.

Ritonavir dosed as an antiretroviral agent

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases.
Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

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

Effects on the electrocardiogram

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

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

Resistance

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

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

Clinical pharmacodynamic data

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

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

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

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

Paediatric use
In an open label study 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 dose 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.

Table 7. Ritonavir dosing regimen

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

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

Effects of food on oral absorption

Food slightly decreases the bioavailability of the ritonavir tablet. Administration of a single 100 mg dose of ritonavir 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 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/m^2 twice daily. Ritonavir concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m^2) 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 studies 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 studies.

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 dose. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dose.

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
Silica, colloidal anhydrous
Sodium chloride
Sodium stearyl fumarate

Film-coating

Hypromellose
Titanium dioxide (E171)
Macrogols
Hydroxypropylcellulose
Talc
Iron oxide yellow (E172)
Silica, colloidal anhydrous
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years
For HDPE bottle: After first opening, use within 45 days.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottle with polypropylene screw cap with aluminium induction sealing liner wad and a desiccant.
Pack sizes: 30, 90, 100 and multipack containing 90 (3 bottles of 30) film-coated tablets.
OPA/Alu/PVC-Alu blister pack containing 30 and 90 tablets.
OPA/Alu/PVC-Alu perforated unit dose blister pack containing 30 x 1, 90 x 1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited t/a Mylan
Station Close, Potters Bar,
EN6 1TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04569/2012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/11/2024

10 DATE OF REVISION OF THE TEXT

06/11/2024