ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 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 Viatris 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

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

Ritonavir Viatris 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.				

Co-administered medicinal product	Dose of co-administered medicinal product (mg)	Dose of ritonavir (mg)	Medicinal product assessed	AUC	C_{min}
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 39%	ND
	750, single	500 q12 h	Nelfinavir	↑ 152%	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily.				
Saquinavir	1,000 q12 h	100 q12 h	Saquinavir[4]	↑ 15-fold	↑ 5-fold
			Ritonavir	↔	↔
	400 q12 h	400 q12 h	Saquinavir[4]	↑ 17-fold	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be given in combination with ritonavir. Ritonavir 100 mg twice daily with saquinavir 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	↑ 11 fold	↑ 29 fold
			Ritonavir	↓ 40%	ND

Co-administered medicinal product	Dose of co-administered medicinal product (mg)	Dose of ritonavir (mg)	Medicinal product assessed	AUC	C_{min}
	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 Norbuprenorphine Glucuronide metabolites	16 q24 h	100 q12 h	↑ 57% ↑ 33% ↔	↑ 77% ↑ 108% ↔
	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 contraindicated (see section 4.3).			

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}
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 administering ceritinib with ritonavir. Refer to the ceritinib SmPC for dose adjustment recommendations. Monitor for ADRs related to ceritinib.			

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}
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 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			

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}
	not recommended (see section 4.4 and refer to the vorapaxar SmPC).			
Warfarin S-Warfarin R-Warfarin	5, single dose	400 q12 h	 ↑ 9% ↑ 33%	 ↓ 9% ↔
	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 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			

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}
	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.			
Voriconazole	200 q12 h 200 q12 h	400 q12 h 100 q12 h	↓ 82% ↓ 39%	↓ 66% ↓ 24%
	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole is **contraindicated** due to reduction in voriconazole concentrations (see section 4.3). Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.			

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}
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 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.			

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}
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).			
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				

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}
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%
	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.			

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}
	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, flurazepam, oral and parenteral midazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If ritonavir			

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}
	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.			
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			

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}
	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				
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 Common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia 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 Common Rare	Pruritus, rash (including erythematous and maculopapular) Acne Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common Common	Arthralgia and back pain Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common Uncommon Not known	Increased urination, renal impairment (e.g. oliguria, elevated creatinine) Acute renal failure Nephrolithiasis
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common Common	Fatigue including asthenia, flushing, feeling hot Fever, weight loss
Investigations	Common Uncommon	Increased amylase, decreased free and total thyroxin 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 national reporting system listed in Appendix V.

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 packaging 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

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/001
EU/1/17/1242/002
EU/1/17/1242/003
EU/1/17/1242/004

EU/1/17/1242/005
EU/1/17/1242/006
EU/1/17/1242/007
EU/1/17/1242/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal: 22 August 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Mylan Hungary Kft./Mylan Hungary Ltd.
Mylan utca 1
2900 Komarom
HUNGARY

Mylan Germany GmbH
Zweigniederlassung Bad Homburg v. d. Hoehe,
Benzstrasse 1,
Bad Homburg v. d. Hoehe,
Hessen, 61352,
GERMANY

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON HDPE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of ritonavir.

3. LIST OF EXCIPIENTS

High in sodium – see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
90 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 45 days.

Open date: _____

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/001 30 film-coated tablets
EU/1/17/1242/002 90 film-coated tablets
EU/1/17/1242/003 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ritonavir Viatris

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of ritonavir.

3. LIST OF EXCIPIENTS

High in sodium – see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
90 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 45 days.

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/001 30 film-coated tablets
EU/1/17/1242/002 90 film-coated tablets
EU/1/17/1242/003 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ritonavir Viatris

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of ritonavir.

3. LIST OF EXCIPIENTS

High in sodium – see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 45 days.

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ritonavir Viatris

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of ritonavir.

3. LIST OF EXCIPIENTS

High in sodium – see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets. Component of a multipack can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 45 days.

Open date: _____

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of ritonavir.

3.LIST OF EXCIPIENTS

High in sodium – see leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
90 film-coated tablets
30 x 1 film-coated tablets (unit dose)
90 x 1 film-coated tablets (unit dose)

5.METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

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

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

11.NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart,
Dublin 15,
DUBLIN,
Ireland

12.MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1242/005 30 film-coated tablets
EU/1/17/1242/006 90 film-coated tablets
EU/1/17/1242/007 30 x 1 film coated tablets (unit dose)
EU/1/17/1242/008 90 x 1 film coated tablets (unit dose)

13.BATCH NUMBER

Lot

14.GENERAL CLASSIFICATION FOR SUPPLY

15.INSTRUCTIONS ON USE

16.INFORMATION IN BRAILLE

Ritonavir Viatris

17.UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18.UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ritonavir Viatris 100 mg film-coated tablets
ritonavir

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

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

What is in this leaflet

1. What Ritonavir Viatris is and what it is used for

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

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

2. What you need to know before you or your child takes Ritonavir Viatris

Do not take Ritonavir Viatris
- if you are allergic to ritonavir or any of the other ingredients of this medicine (see section 6).
- if you have severe liver disease.
- if you are currently taking any of the following medicines:
  - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription);
  - amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine (used to correct irregular heartbeats);
  - dihydroergotamine, ergotamine (used to treat migraine headache);
  - ergonovine, methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion);
  - clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam (used to help you sleep and/or relieve anxiety);
  - clozapine, pimozide, (used to treat abnormal thoughts or feelings);
  - quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
  – lurasidone (used to treat depression);
  – ranolazine (used to treat chronic chest pain [angina]);
  - pethidine, propoxyphene (used to relieve pain);
  - cisapride (used to relieve certain stomach problems);

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

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

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

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

Warnings and precautions

Talk to your doctor before taking Ritonavir Viatris.

Important information
- If Ritonavir Viatris is taken in combination with other antiretroviral medicines, it is important that you also carefully read the leaflets that are provided with these other medicines. There may be additional information in those leaflets about situations when ritonavir should be avoided. If you have any further questions about Ritonavir Viatris (ritonavir) or the other medicines prescribed, please ask your doctor or pharmacist.
- Ritonavir is not a cure for HIV infection or AIDS.
- People taking ritonavir may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of your doctor while taking Ritonavir Viatris.

Tell your doctor if you have/had:

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

- **Kidney (renal) disease,** since your doctor may need to check the dose of your other medicines (such as protease inhibitors).

Tell your doctor if you experience:

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

Children and adolescents

Ritonavir Viatris is not recommended in children below 2 years of age.

Other medicines and Ritonavir Viatris

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

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

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

- **Sildenafil or tadalafil** for impotence (erectile dysfunction).
  The dose and/or frequency of use of these medicines may need to be reduced to avoid hypotension and prolonged erection. You must not take Ritonavir Viatris with sildenafil if you suffer from pulmonary arterial hypertension (see also section 2. **What you need to know before you or your child takes Ritonavir Viatris**). Tell your doctor if you are taking tadalafil for pulmonary arterial hypertension.

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

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

- amphetamine or amphetamine derivatives;
- antibiotics (e.g. erythromycin, clarithromycin);
- anticancer treatments (e.g. abemaciclib, afatinib, apalutamide, ceritinib, encorafenib, dasatinib, ibrutinib, nilotinib, venetoclax, vincristine, vinblastine);
- medicines used to treat low blood platelet count (e.g. fostamatinib)
- anticoagulants (e.g. dabigatran etexilate, edoxaban, rivaroxaban, vorapaxar, warfarin);
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole);
- antihistamines (e.g. loratadine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir) non-nucleoside reverse transcriptase inhibitors (NNRTI) (delavirdine, efavirenz, nevirapine), and others (didanosine, maraviroc, raltegravir, zidovudine);
- anti-tuberculosis medicine (bedaquiline and delamanid);
- antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (e.g. glecaprevir/pibrentasvir and simeprevir);
- anxiety medicine, buspirone;
- asthma medicine, theophylline, salmeterol;
- atovaquone, a medicine used to treat a certain type of pneumonia and malaria;
- buprenorphine, a medicine used for the treatment of chronic pain;
- bupropion, a medicine used to help you stop smoking;
- epilepsy medicines (e.g. carbamazepine, divalproex, lamotrigine, phenytoin);
- heart medicines (e.g. disopyramide, mexiletine and calcium channel antagonists such as amlodipine, diltiazem and nifedipine);
- immune system (e.g. cyclosporine, tacrolimus, everolimus);
- levothyroxine (used to treat thyroid problems)
- morphine and morphine-like medicines used to treat severe pain (e.g. methadone, fentanyl);

- sleeping pills (e.g. alprazolam, zolpidem) and also midazolam administered by injection;
- tranquillisers (e.g. haloperidol, risperidone, thioridazine);
- colchicine, a treatment for gout.

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

Taking Ritonavir Viatris with food and drink

Ritonavir Viatris tablets should be taken with food.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, it is very important that you ask your doctor for advice before taking this medicine.

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

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

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

Driving and using machines

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

Ritonavir Viatris contains sodium

This medicine contains 87.75 mg of sodium in each tablet. This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need five or more tablets daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

3. How to take Ritonavir Viatris

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

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

Recommended doses of Ritonavir Viatris are:

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

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

Other forms of this medicine may be more appropriate for children who have difficulty swallowing tablets.

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

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

If you take more Ritonavir Viatris than you should

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

If you forget to take Ritonavir Viatris

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

If you stop taking Ritonavir Viatris

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

4. Possible side effects

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

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

Very common: may affect more than 1 in 10 people

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

Common: may affect up to 1 in 10 people

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

Uncommon: may affect up to 1 in 100 people

- heart attack
- diabetes
- kidney failure

Rare: may affect up to 1 in 1,000 people

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

Not known: frequency cannot be estimated from the available data

- kidney stones

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

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

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

There have been reports of muscle pain, tenderness or weakness, particularly when taking medicines to lower cholesterol in combination with antiretroviral therapy, including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop taking the medicine, contact your doctor as soon as possible or go to the Accident and Emergency Department of your nearest hospital.

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

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

Reporting of side effects

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

5. How to store Ritonavir Viatris

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

Do not use this medicine after the expiry date on the carton or bottle label after 'EXP'. The expiry date refers to the last day of that month.

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

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

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

6. Contents of the pack and other information

What Ritonavir Viatris contains

- The active substance is ritonavir. Each film-coated tablet contains 100 mg ritonavir.
- The other tablet ingredients are: copovidone, sorbitan laurate, colloidal anhydrous silica, sodium chloride, sodium stearyl fumarate see section 2 'Ritonavir Viatris contains sodium'.
- The tablet coating is composed of: hypromellose, titanium dioxide (E171), macrogols, hydroxypropylcellulose, talc, iron oxide yellow (E172), colloidal anhydrous silica, polysorbate 80.

What Ritonavir Viatris looks like and contents of the pack

Ritonavir Viatris film-coated tablets are yellow, capsule shaped, biconvex, beveled edge and marked with 'M163' on one side and blank on the other.

Ritonavir Viatris film-coated tablets are available in plastic bottles with screw caps and aluminium sealing liner wads, containing 30, 90 or 100 tablets and in multipacks of 90 tablets comprising 3 bottles, each containing 30 tablets. The bottles also contain a desiccant. Do not eat the desiccant.

Also available in blister pack containing 30 and 90 tablets and in perforated unit dose blister packs containing, 30 x 1 and 90 x 1 tablets.

Not all pack sizes may be marketed.

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