WHO-PQ RECOMMENDED
SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA741 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg ritonavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White-coloured, oval-shaped, shallow, film-coated tablets debossed with "25" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA741 trade name] is indicated as a pharmacokinetic enhancer for protease inhibitors when these are used in combination therapy with other antiretroviral agents for the treatment of HIV-1 infected patients.

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

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and breastfeeding, to allow full access to all relevant information.

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection.

Posology

[HA741 trade name] should be taken with food. The tablets should be swallowed whole and not be chewed, broken or crushed.

As [HA741 trade name] is used as a pharmacokinetic enhancer with other protease inhibitors, the product information for the particular protease inhibitor must be consulted.

The following HIV-1 protease inhibitors can be used with ritonavir as a pharmacokinetic enhancer at the noted doses.

Adults and adolescents:

- Amprenavir 600 mg twice daily with ritonavir 100 mg twice daily.
- Atazanavir 300 mg once daily with ritonavir 100 mg once daily.
- Fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily.
- Lopinavir co-formulated with ritonavir (lopinavir/ritonavir) 400 mg/100 mg or 800 mg/200 mg.
- Saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily in 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 1000 mg twice daily with ritonavir 100 mg twice daily in ART-naïve patients.
- Tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. Tipranavir with ritonavir should not be used in treatment-naïve patients.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

– 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 product information 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.

For use in adults, more suitable formulations containing a higher amount of the active substance, i.e. 100 mg tablets, may be available.

Paediatric patients:

In children weighing from 14 to 25 kg, the recommended dose is either 100 mg ritonavir (4 tablets) once a day or 50 mg ritonavir (2 tablets) twice a day.

In children weighing from 25 to 35 kg, the recommended dose is 100 mg ritonavir once or twice per day, depending on the concurrently used protease inhibitor. In these patients, formulations containing a higher amount of the active substance, i.e. 100 mg tablets, may be used.

For children who are undergoing anti-tuberculosis treatment with rifampicin, higher dosages of ritonavir may be needed for pharmacokinetic enhancement of the combined protease inhibitor. Please refer to the product information of the protease inhibitors approved for co-administration with ritonavir.

Special populations

Renal impairment:

Depending on the specific protease inhibitor with which it is co-administered, ritonavir may be appropriate for use with caution in patients with renal insufficiency. For specific dosing information in patients with renal impairment, refer to the product information of the co-administered protease inhibitor.

Hepatic impairment:

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

Paediatric population:

[HA741 trade name] should only be used in children who can swallow tablets whole. Other, more suitable formulations may be available for children not able to swallow tablets whole.

4.3 Contraindications

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

Consult the product information of the co-administered medicine for other possible contraindications.

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

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

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

Drug class	Drugs within class	Rationale
Concomitant drug levels increased or decreased		
α1-Adrenoreceptor Antagonist	alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension (see section 4.5).
Analgesics	pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antianginal	ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
Anticancer	neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity (see section 4.5).
	venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumor lysis syndrome at the dose initiation and during the dose-titration phase (see section 4.5).
Antiarrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotic	fusidic acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antihistamines	astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Anti-gout	colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antipsychotics/ Neuroleptics	lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions (see section 4.5).
	clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents.
	quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility agent	cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent.

Drug class	Drugs within class	Rationale
Concomitant drug levels increased or decreased		
Lipid-modifying agents HMG Co-A Reductase Inhibitors	lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis (see section 4.5).
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	Increased plasma concentrations of lomitapide (see section 4.5).
PDE5 inhibitor	avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
	sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope). See section 4.4 and section 4.5 for co-administration of sildenafil in patients with erectile dysfunction.
	vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
Sedatives/hypnotics	clorazepate, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, 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 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

Patients receiving ritonavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by health care providers experienced in the treatment of these associated HIV diseases.

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

As ritonavir is used as a pharmacokinetic enhancer with other protease inhibitors, full details on the warnings and precautions relevant to that particular protease inhibitor should be considered.

Some of the below warnings originate from the use of ritonavir as antiretroviral agent at higher doses than those recommended for pharmacokinetic enhancement. The effects of ritonavir when used as a pharmacokinetic enhancer might hence be less pronounced.

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.

Patients with 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 half of the reported cases, protease inhibitors treatment was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, but the mechanism of action has not been elucidated. Patients with haemophilia should therefore be made aware of the possibility of increased bleeding.

Weight, blood lipids and glucose

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is some evidence of a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring blood lipids and glucose, consult 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

When starting combination antiretroviral therapy (CART) in patients with severe immune deficiency, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravate symptoms. Typically, such reactions occur within the first weeks or months of starting CART. Relevant examples are cytomegalovirus retinitis, generalised or focal mycobacterial infections and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treated when necessary.

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

Liver disease

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

Patients with liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal disease

Since the renal clearance of ritonavir is negligible, decrease in the total body clearance is not expected in patients with renal impairment. For specific dosing information in patients with renal impairment, refer to the product information of the co-administered protease inhibitor. See also section 4.2.

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

Osteonecrosis

Cases of osteonecrosis have been reported particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. The aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, high body mass index). Patients should be advised to seek medical advice if they have 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

Full details on the warnings and precautions relevant to the protease inhibitor ritonavir is used with must be considered, therefore section 4.4 of the product information for the particular protease inhibitor must be consulted to determine if the information below is applicable. Furthermore, some information may only apply to ritonavir used as an antiretroviral agent.

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

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

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

Colchicine: Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see sections 4.3 and 4.5).

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

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

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

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

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

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

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

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 product information).

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 product information).

Saquinavir: Doses of ritonavir higher than 100 mg twice daily should not be used. Higher doses of ritonavir have been shown to be associated with an increased incidence of adverse reactions.

Co-administration of saquinavir and ritonavir has led to severe adverse reactions, mainly diabetic ketoacidosis and liver disorders, especially in patients with pre-existing liver disease.

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Medicinal products that affect ritonavir levels

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

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

Interaction table

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. The product information of the medicines used concomitantly with ritonavir should be consulted.

Medicinal Product Interactions – Ritonavir with Protease Inhibitors

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	Drug assessed	AUC	Cmin
Amprenavir	600 q12h	100 q12h	Amprenavir[1]	↑64%	↑5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. For further information, physicians should refer to the amprenavir product information.				
Atazanavir	300 q24h	100 q24h	Atazanavir	↑86%	↑11 fold
			Atazanavir[2]	↑2 fold	↑3-7 fold
	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. For further information, physicians should refer to the product information for atazanavir products.				

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

ND: Not determined.

1. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.
2. Based on cross-study comparison to 400 mg atazanavir once daily alone.
3. Based on cross-study comparison to 800 mg indinavir three times daily alone.
4. Based on cross-study comparison to 600 mg saquinavir three times daily alone.

Medicinal product interactions – ritonavir with antiretroviral agents other than protease inhibitors

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	Drug assessed	AUC	Cmin
Didanosine	200 q12h	600 q12h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on an empty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Delavirdine	400 q8h	600 q12h	Delavirdine[1]	↔	↔
			Ritonavir	↑ 50%	↑ 75%
	Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, dose reduction of ritonavir may be considered.				
Efavirenz	600 q24h	500 q12h	Efavirenz	↑ 21%	
			Ritonavir	↑17%	
	A higher frequency of adverse reactions (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) has been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Maraviroc	100 q12h	100 q12h	Maraviroc	↑ 161%	↑ 28%
	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the product information for maraviroc.				
Nevirapine	200 q12h	600 q12h	Nevirapine	↔	↔
			Ritonavir	↔	↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either nevirapine or ritonavir.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.				
Zidovudine	200 q8h	300 q6h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.				

ND: Not determined

1. Based on parallel group comparison.

Ritonavir effects on non-antiretroviral co-administered medicinal products

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
Alpha1-Adrenoreceptor Antagonist				
Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore contraindicated (see section 4.3).			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the product information of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, piroxicam, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine, piroxicam, and propoxyphene and is therefore contraindicated (see section 4.3).			
Fentanyl	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.			
Methadone[1]	5, single dose	500 q12h,	↓ 36%	↓ 38%
	Increased methadone dose may be necessary when concomitantly administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.			
Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Antianginal				
Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).			
Antiarrthymics				
Amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecanide, propafenone, and quinidine and is therefore contraindicated (see section 4.3).			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
Lidocaine	Coadministration may increase lidocaine exposure and a dose adjustment may be needed. The clinical effect should be monitored.			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND
	0.4 single oral dose	200 q12h, 13 days	↑ 22%	↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antriretroviral agent or as a pharmacokinetic enhancer. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops (see section 4.4).			
Antiasthmatic				
Theophylline[1]	3 mg/kg q8h	500 q12h	↓ 43%	↓ 32%
	An increased dose of theophyline may be required when co- administered with ritonavir, due to induction of CYP1A2.			
Anticancer agents				
Afatinib	20 mg, single dose	200 q12h/1h before	↑ 48%	↑ 39%
	40 mg, single dose	200 q12h/ coadministered	↑ 19%	↑ 4%
	40 mg, single dose	200 q12h/6h after	↑ 11%	↑ 5%
	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with [HA741 trade name] (refer to the afatinib product information). 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 product information for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.			
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of ritonavir and potential loss of virologic response. In addition, serum concentrations may be increased when co-administered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of ritonavir with apalutamide is not recommended.			
Ceritinib	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with ritonavir. Refer to the ceritinib product information for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.			
Dasatinib, nilotinib, vincristine, vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse reactions.			
Encorafenib	Serum concentrations may be increased when co-administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.			
Fostamatinib	Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension, or diarrhoea. Refer to the fostamatinib product information			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
	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 tumour 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 product information). 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 product information for dosing instructions).			
Anticoagulants				
Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			
Vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with ritonavir is not recommended (see section 4.4 and refer to the vorapaxar product information).			
Warfarin	5, single dose	400 q12h		
S-Warfarin			↑ 9%	↓ 9%
R-Warfarin			↓ 33%	↔
	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Anticonvulsants				
Carbamazepine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of carbamazepine. Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is concomitantly administered with ritonavir. A dose adjustment may be needed.			
Divalproex, lamotrigine, phenytoin	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are concomitantly administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.			
Oxcarbazepine	Coadministration may decrease exposure of the antiretroviral drug, although to a moderate extent. A dose adjustment may be needed. Monitor clinical effect. Alternative anticonvulsants should be considered.			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Desipramine	100, single oral dose	500 q12h	↑ 145%	↑ 22%
	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15 and 67%, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir dosed as an antiretroviral agent.			
Trazodone	50, single dose	200 q12h	↑ 2.4-fold	↑ 34%
	An increase in the incidence in trazodone-related adverse reactions was noted when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If trazodone is co-administered with ritonavir, the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability.			
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition) in patients with renal and/or hepatic impairment (see sections 4.3 and 4.4). Refer to the colchicine product 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 antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly administered with ritonavir.			
Anti-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).			
Rifabutin	Co-administration increases rifabutin exposure. 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 product information of the co-administered protease inhibitor should be consulted for specific recommendations. Due to the limited safety data with this dose and combination, patients should be closely monitored for rifabutin-related toxicities (i.e. uveitis or neutropenia). 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			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
	have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The effect of ritonavir on rifampicin is not known.			
Voriconazole	200 q12h	100 q12h	↓ 39%	↓ 24%
	Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.			
Atovaquone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.			
Bedaquiline	No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4 and refer to the bedaquiline product information).			
Clarithromycin	500 q12h	200 q8h	↑ 77%	↑ 31%
14-OH clarithromycin metabolite			↓ 100%	↓ 99%
	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.			
Delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid product information).			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin and itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is used concomitantly administered with ritonavir.			
Ketoconazole	200 daily	500 q12h	↑ 3.4-fold	↑ 55%
	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Sulfamethoxazole/ Trimethoprim[1]	800/160, single dose	500 q12h	↓ 20% / ↑ 20%	↔
	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
	should not be necessary.			
Antipsychotics/Neuroleptics				
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 4.3).			
Haloperidol, risperidone, thioridazine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.3).			
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.			
β2-agonist (long acting)				
Salmetarol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmetarol is expected. Therefore concomitant use is not recommended.			
Calcium channel antagonists				
Amlodipine, diltiazem, nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
Endothelin antagonists				
Bosentan	Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentr ations (C_{max}) and area under the curve (AUC).			
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 product information).			
Ergot Derivatives				
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3).			
GI motility agent				
Cisapride	Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride and is therefore contraindicated (see section 4.3).			
HCV Direct Acting Antiviral				
Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.			
HMG Co-A Reductase Inhibitors				
Atorvastatin, fluvastatin,	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism,			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
lovastatin, pravastatin, rosuvastatin, simvastatin	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				
HRT Dydrogesterone, levonorgestrel, medroxyprogesterone (oral), norethisterone (norethindrone)	Coadministration may increase comedication exposure. The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.			
Drospirenone	Coadministration may increase drospirenone exposure. The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary. Clinical monitoring is recommended due to the potential risk for hyperkalaemia.			
Estradiol	Coadministration may decrease comedication exposure. Monitor for signs of hormone deficiency.			
Ethinyl estradiol	50 µg, single dose	500 q12h	↓ 40%	↓ 32%
	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives (see section 4.4).			
Immunosupressants				
Cyclosporine, tacrolimus, everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			
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 product information for lomitapide) (see section 4.3).			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
Phosphodiesterase (PDE5) inhibitors				
Avanafil	50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
	Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).			
Sildenafil	100, single dose	500 q12h	↑ 11-fold	↑ 4-fold
	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours (see also section 4.4). Concomitant use of sildenafil with ritonavir is contraindicated in pulmonary arterial hypertension patients (see section 4.3).			
Tadalafil	20, single dose	200 q12h	↑ 124%	↔
	The concomitant use of tadalafil 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 product information.			
Vardenafil	5, single dose	600 q12h	↑ 49-fold	↑ 13-fold
	The concomitant use of vardenafil with ritonavir is contraindicated (see section 4.3).			
Sedatives/hynoptics				
Clorazepate, estazolam, flurazepam, oral and parenteral midazolam and triazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, estazolam and flurazepam and is therefore contraindicated (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with ritonavir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of ritonavir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, ritonavir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of ritonavir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If ritonavir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			
Diazepam	Coadministration may increase diazepam exposure and a dose adjustment may be needed. The clinical effect should be monitored.			
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).			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
Pethidine	50, oral single dose	500 q12h	↓ 62%	↓ 59%
Norpethidine metabolite			↑ 47%	↑ 87%
	The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (eg, seizures), see section 4.3.			
Alprazolam	1, single dose	200 q12h, 2 days	↑2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.			
Sleeping agent				
Zolpidem	5	200, 4 doses	↑ 28%	↑ 22%
	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.			
Smoke cessation				
Bupropion	150	100 q12h	↓ 22%	↓ 21%
	150	600 q12h	↓ 66%	↓ 62%
	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.			
Steroids				
Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression 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 that is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids, progressive dose reduction may be			

Co-administered drug	Dose Co-administered drug (mg)	Ritonavir dose (mg)	AUC	Cmax
	required over a longer period.			
Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.			
Prednisolone	20	200 q12h	↑ 28%	↑ 9%
	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.			
Thyroid hormone replacement therapy				
Levorthyroxine	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 with levothyroxine at least the first month after starting and/or ending ritonavir treatment.			

ND: Not determined
1. 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.

Further information regarding medicinal product interactions when ritonavir is used a pharmacokinetic enhancer is also contained in the product information of the coadministered protease inhibitor.

Proton pump inhibitors and H2-receptor antagonists (e.g. omeprazole or ranitidine) may reduce concentrations for co-administered protease inhibitors. For specific information regarding the impact of co-administration of acid-reducing agents, refer to the product information 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 breastfeeding

Pregnancy

A large number of pregnant women (corresponding to 6100 live births) were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. These data largely refer to exposure of ritonavir used as a booster for protease inhibitors in combination therapy. There was no increase in the rate of birth defects compared to rates in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity (see section 5.3).

[HA741 trade name] can be used during pregnancy if clinically needed.

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

Breast-feeding

Ritonavir has been detected in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the medicine on milk production. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

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 borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

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

The following adverse reactions were reported from clinical trials and post-marketing experience in adult patients with ritonavir dosed as antiretroviral agent.

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

Adverse reactions in clinical trials and post-marketing

MedDRA system organ class Frequency category	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	hypersenstitivity including urticaria, and face oedema
rare	anaphylaxis
Metabolism and nutrition disorders	
common	hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually

	associated with gastrointestinal symptoms)
uncommon	diabetes mellitus
rare	hyperglycaemia
Nervous system disorders	
very common	dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy
common	insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	
common	blurred vision
Cardiac disorders	
uncommon	myocardial infarction
Vascular disorders	
common	hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
very common	pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	
very common	abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia
common	anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	
common	hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	
very common	pruritus, rash (including erythematous and maculopapular)
common	acne
rare	Stevens Johnson syndrome, toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
very common	arthralgia and back pain
common	myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	
common	increased urination, renal impairment (e.g. oliguria, elevated creatinine)
uncommon	acute renal failure
not known	nephrolithiasis
Reproductive system and breast disorders	
common	menorrhagia
General disorders and administration site conditions	

very common 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

Hepatotoxicity

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).

Immune reconstitution inflammatory syndrome

In patients with severe immune deficiency at the time of initiation of 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 time to onset is more variable and these events can occur many months after starting treatment (see section 4.4).

Pancreatitis

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridaemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis (see section 4.4).

Osteonecrosis

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

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

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

Management

There is no specific antidote for overdose with ritonavir. Treatment of overdose with ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of

the patient. Due to the solubility characteristics and possibility of transintestinal elimination, it is proposed that management of overdose could entail gastric lavage and administration of activated charcoal. Since ritonavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 darunavir is generally achieved with ritonavir doses of 100 mg daily to 200 mg twice daily. For additional information on the effect of ritonavir on co-administered protease inhibitor metabolism, see section 4.5 and consult the product information of the particular co-administered protease inhibitor.

Effects on the electrocardiogram

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

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

Resistance

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

Reduction in the antiretroviral activity of ritonavir is primarily associated with the protease mutations V82A/F/T/S and I84V. Accumulation of other mutations in the protease gene (including at positions 20, 33, 36, 46, 54, 71, and 90) can also contribute to ritonavir resistance. In general, as mutations associated with ritonavir resistance accumulate, susceptibility to select other protease inhibitors 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 efficacy and safety data

Ritonavir was the first protease inhibitor (approved in 1996) for which efficacy was proven in a study with clinical endpoints. 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. 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).

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [HA741 trade name].

The absorption characteristics of a proportionally similar medicine (Ritonavir 100 mg tablets of Cipla Ltd.) have been determined after administration of 2 tablets (each containing 100 mg ritonavir) in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	2903 ± 914 ng/ml
Area under the curve (AUC_{0-t}), a measure of the extent of absorption	19620 ± 7548 ng·h/ml
Time to attain maximum concentration (t_{max})	4.16 ± 1.05 h

* Arithmetic mean

Pharmacokinetics of Ritonavir

	Ritonavir
General	
Absorption	
Oral bioavailability	
Food effect	Food slightly decreases the bioavailability of ritonavir tablets. A single oral dose of ritonavir 100 mg 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	
Volume of distribution (mean ± SD)	After single 600 mg dose: approximately 20–40L
Plasma proteinbinding *in vitro*	Approximately 98–99% and is constant over the concentration range of 1–100 µg/ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.
Tissue distribution	Studies in rats showed highest concentrations of ritonavir in the liver, adrenals, pancreas, kidneys and thyroid. Tissue to plasma ratios of approximately 1 measured in rat lymph nodes suggest that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.
Metabolism	
	Primarily oxidative metabolism according to animal studies and *in vitro* experiments with human liver microsomes (HLMs). Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite.

	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).
Active metabolite(s)	M-2 has antiviral activity similar to that of parent compound but its AUC was approximately 3% of the AUC of parent compound.
Elimination	
Elimination half life	
Mean systemic clearance (Cl/F)	
% of dose excreted in urine	Renal clearance of ritonavir is negligible.
% of dose excreted in faeces	86%; part of which is expected to be unabsorbed ritonavir.
Drug interactions *(in vitro)*	
Transporters	P-glycoprotein and anion-transporting polypeptides
Metabolising enzymes	Hepatic CYP system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform.

Pharmacokinetics in special populations

Paediatric population

Ritonavir steady-state pharmacokinetic parameters were evaluated in HIV-infected children above 2 years of age receiving doses ranging from 250 mg/m² twice daily to 400 mg/m² twice daily. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in paediatric patients were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. Across dose groups, ritonavir oral clearance ($CL/F/m^2$) was approximately 1.5 to 1.7 times faster in paediatric patients above 2 years of age than in adult subjects.

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

Elderly

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.

Gender

No clinically significant differences in AUC or C_{max} were noted between males and females.

Renal impairment

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.

Hepatic impairment

After multiple dosing 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.

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. All thyroid changes were reversible upon discontinuation of ritonavir. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:	Colloidal silicon dioxide
	Anhydrous dibasic calcium phosphate
	Copovidone
	Sorbitan monolaurate
	Sodium stearyl fumarate
Seal coating:	Hypromellose
Film coat:	Titanium dioxide
	Hypromellose
	Macrogol/polyethylene glycol
	Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White opaque HDPE bottle with white opaque non-CRC HDPE cap and rayon sani coil.

Pack size: 60 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Cipla Ltd.

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Peninsula Business Park

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Lower Parel

Mumbai: 400013

India

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA741

9. DATE OF PREQUALIFICATION

30 November 2021

10. DATE OF REVISION OF THE TEXT

January 2022

References

General reference sources for this SmPC include:

World Health Organization (2021) Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, available at https://www.who.int/publications/i/item/9789240031593

World Health Organization (2016) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd ed. World Health Organization https://apps.who.int/iris/handle/10665/208825

European SmPC, Norvir, available at: https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_en.pdf

All weblinks were last accessed on 16 January 2022

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines