# 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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

# 1. NAME OF THE MEDICINAL PRODUCT

[HA467 trade name]†

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of ritonavir.

*Excipients with potential clinical effect*

Each tablet also contains 3.82 mmol (87.76 mg) sodium.

# 3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, capsule-shaped, film-coated tablets. The tablets have 'M163' debossed (stamped into) one side and are plain on the other side. There is no score line.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[HA467 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.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

## 4.2 Posology and method of administration

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

***Posology***

As [HA467 trade name] is used as a pharmacokinetic enhancer with other protease inhibitors, the product information of the co-administered protease inhibitor must be consulted for appropriate information on dosage of ritonavir.

*Adults and adolescents weighing 35 kg or more:*

In adults and adolescents, the recommended dose is 100 mg ritonavir (one tablet) once or twice a day, depending on the concurrently used protease inhibitor.

*Children:*

*In children weighing from 25 to 35 kg*, the recommended dose is 100 mg ritonavir (one tablet) once or twice per day, depending on the concurrently used protease inhibitor.

*In children weighing from 14 to less than 25 kg*, other formulations containing lower amounts of ritonavir (e.g. 25 mg) may be more appropriate.

*Patients also receiving rifampicin for tuberculosis*

For patients 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.

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† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.
** Previously known as Matrix Laboratories Limited.

***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.

*Children:*

[HA467 trade name] should not be used in children weighing less than 25 kg. For these patients, more suitable formulations containing a lower amount of the active substance may be available.

***Method of administration***

[HA467 trade name] should be taken with food. The tablets should be swallowed whole and not be chewed, broken or crushed.

## 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, especially at higher doses. 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.

| 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 tumour lysis syndrome at the dose initiation and during the |

| Drug class | Drugs within class | Rationale |
|---|---|---|
| **Concomitant drug levels increased or decreased** | | |
| | | dose-titration phase. Contraindicated during initial dose titration of venetoclax due to increased risk of tumour lysis syndrome (see section 4.5 for patients who have completed dose titration and are on a steady daily dose). |
| 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 Contraindicated in patients with renal and/or hepatic impairment (see section 4.5 for colchicine doses in patients with normal hepatic and renal impairment). |
| 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. |
| Lipid-modifying agents<br>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 4.5). |
| | 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 4.5 for co-administration of sildenafil in patients with erectile dysfunction. |
| | vardenafil | Increased plasma concentrations of vardenafil (see section |

| Drug class | Drugs within class | Rationale |
|---|---|---|
| **Concomitant drug levels increased or decreased** | | |
| | | 4.5). |
| Sedatives/hypnotics | clorazepate, estazolam, diazepam, flurazepam, oral midazolam and triazolam | Increased plasma concentrations of clorazepate, estazolam, diazepam, 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.

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 2$^{nd}$ or 3$^{rd}$ 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).

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.

For precautionary information on other medicinal products that interact with ritonavir, see section 4.5.

*Excipients*

Each tablet contains 3.82 mmol (87.76 mg) sodium, equivalent to about 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

## 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 |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | Drug assessed | AUC | Cmin |
|---|---|---|---|---|---|
| | 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. The use of higher ritonavir doses may alter the safety profile of atazanavir (cardiac effects, hyperbilirubinaemia) and therefore is not recommended. However, when atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered. For further information, physicians should refer to the product information for atazanavir products. | | | | |
| 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. The use of higher ritonavir doses might alter the safety profile of the combination and therefore is not recommended. 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. 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 an increased incidence of adverse reactions.<br>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 | | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | Drug assessed | AUC | Cmin |
|---|---|---|---|---|---|
| | 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.<br>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. Co-administration of tipranavir with 200 mg of ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, some fatal. Extra care is needed in patients with hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.<br>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<br>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. When atazanavir with ritonavir is co-administered with efavirenz, a dose increase of ritonavir to 200 mg once daily could be considered | | | | |
| 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 | | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | Drug assessed | AUC | Cmin |
|---|---|---|---|---|---|
| | 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 | | | |
| **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) | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | 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). | | | |
| Lidocaine | Co-administration 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. 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.<br>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. | | | |
| **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/ co-administered | ↑ 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 | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | on the timing of ritonavir administration. Caution should be exercised in administering afatinib with [HA467 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.<br>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.<br>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 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.<br>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).<br>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. | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| Vorapaxar | Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with ritonavir is not recommended (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. | | | |
| 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. | | | |
| Oxcarbamazepine | Co-administration 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. | | | |
| **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. | | | |
| 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 such as nausea, dizziness, hypotension and syncope have been observed when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If trazodone is co-administered with ritonavir, the combination should be used with caution, initiating trazodone at the lowest dosage and monitoring for clinical response and tolerability. | | | |
| **Anti-gout treatments** | | | | |
| Colchicine | Concentrations of colchicine are expected to increase when co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition) in patients with renal | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | and/or hepatic impairment and the combination is contraindicated in such patients (see sections 4.3). A reduction in dose of colchicine is recommended in patients with normal renal and hepatic function if treatment with ritonavir is required. 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). | | | |
| 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 product information of the co-administered protease inhibitor should be consulted for specific recommendations. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV-infected patients. | | | |
| Rifampicin | Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administered with rifampicin, the additional inducing effect of rifampicin (next to that of ritonavir itself) is small and may have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The effect of ritonavir on rifampicin is not known. | | | |
| Voriconazole | 200 q12h | 100 q12h | ↓ 39% | ↓ 24% |
| | Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. | | | |
| Atovaquone | Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir. | | | |
| Bedaquiline | No interaction study is available with ritonavir only. In an interaction study of single-dose bedaquiline and multiple dose lopinavir/ritonavir, the AUC of bedaquiline was increased by 22%. This increase is likely due to ritonavir and a more pronounced effect may be observed during prolonged co-administration. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | (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 (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 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)** | | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| 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. | | | |
| **Contraceptives/HRT** | | | | |
| *HRT*<br>Dydrogesterone, levonorgestrel, medroxyprogesterone (oral), norethisterone (norethindrone) | Co-administration 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 | Co-administration 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 | Co-administration may decrease comedication exposure. Monitor for signs of hormone deficiency. | | | |
| | | | | |
| **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 (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). | | | |
| **HCV Direct Acting Antiviral** | | | | |
| Glecaprevir/pibrentasvir | Seurm concentrations may be increased due to P-glycoprotein, BCRP and OATP1B inhibition by ritonavir.<br>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, 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 | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 4.3).<br>Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended. | | | |
| **Hormonal contraceptive** | | | | |
| Ethinyl estradiol | 50 µg, single dose | 500 q12h | ↓ 40% | ↓ 32% |
| | Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives. | | | |
| **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). | | | |
| **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. Co-administration with ritonavir can substantially increase sildenafil concentrations and may result in associated adverse reactions such as hypotension and prolonged erection. 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. Co-administration with ritonavir can substantially increase tadalafil concentrations and may result in associated adverse reactions such as hypotension and prolonged erection. When tadalafil is used concurrently with ritonavir in patients with pulmonary arterial | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| | 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, diazepam, 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).<br>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- to 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 | Co-administration 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). | | | |
| 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** | | | | |

| Co-administered drug | Dose Co-administered drug (mg) | Ritonavir dose (mg) | AUC | Cmax |
|---|---|---|---|---|
| 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. 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 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. | | | |
| Stimulants | | | | |
| Methamphetamine | Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir | | | |
| 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 co-administered 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 surveillance systems. Animal data have shown reproductive toxicity (see section 5.3).

[HA467 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

***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 diarrhoea, nausea, vomiting, abdominal pain [upper and lower]), neurological disturbances (including paraesthesia and oral paraesthesia) and fatigue/asthenia.

### *Tabulated list of adverse reactions*

The adverse reactions considered related to ritonavir are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (at least 1/10), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare (< 1/10 000).

***Blood and lymphatic system disorders***

| | |
|---|---|
| common | decreased white blood cells, decreased haemoglobin, decreased neutrophils, increased eosinophils, thrombocytopenia |
| uncommon | increased neutrophils |

**Immune system disorders**

| | |
|---|---|
| common | hypersensitivity including urticaria and face oedema |
| rare | anaphylaxis |

**Metabolism and nutrition disorders**

| | |
|---|---|
| common | hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms) |
| uncommon | diabetes mellitus |
| rare | hyperglycaemia |

**Nervous system disorders**

| | |
|---|---|
| Very common | dysgeusia, oral and peripheral paraesthesia, headache, dizziness, peripheral neuropathy |
| common | insomnia, anxiety, confusion, disturbance in attention, syncope, seizure |

**Eye disorders**

| | |
|---|---|
| common | blurred vision |

**Cardiac disorders**

| | |
|---|---|
| uncommon | myocardial infarction |

**Vascular disorders**

| | |
|---|---|
| common | hypertension, hypotension including orthostatic hypotension, peripheral coldness |

**Respiratory, thoracic and mediastinal disorders**

| | |
|---|---|
| very common | pharyngitis, oropharyngeal pain, cough |

**Gastrointestinal disorders**

| | |
|---|---|
| Very common | abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia |
| common | anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis |

**Hepatobiliary disorders**

| | |
|---|---|
| common | hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice) |

**Skin and subcutaneous tissue disorders**

| | |
|---|---|
| Very common | pruritus, rash (including erythematous and maculopapular) |
| common | acne |
| rare | Stevens Johnson syndrome, toxic epidermal necrolysis (TEN) |

**Musculoskeletal and connective tissue disorders**

| | |
|---|---|
| Very common | arthralgia and back pain |

| | |
|---|---|
| common | myositis, rhabdomyolysis, myalgia, myopathy/CPK increased |

**Renal and urinary disorders**

| | |
|---|---|
| common | increased urination, renal impairment (e.g. oliguria, elevated creatinine) |
| uncommon | acute renal impairment |
| Not known | nephrolithiasis |

**Reproductive system and breast disorders**

| | |
|---|---|
| common | menorrhagia |

**General disorders and administration site conditions**

| | |
|---|---|
| Very common | fatigue including asthenia, flushing, feeling hot |
| common | fever, weight loss |

**Investigations**

| | |
|---|---|
| common | increased amylase, decreased free and total thyroxin |
| uncommon | increased glucose, increased magnesium, increased alkaline phosphatase |

***Description of selected adverse reactions***

*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.

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.

***Reporting of suspected adverse reactions***

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

### 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 $\geq$ 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 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

Absorption characteristics of [HA467 trade name] were determined following administration of a single ritonavir 100 mg tablet in healthy volunteers in the fed state as follows:

| **Pharmacokinetic variable** | **Mean value* ± standard deviation** |
|---|---|
| Maximum concentration ($C_{max}$) | 859 ± 382 ng/mL |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 7367 ± 3614 ng·h/mL |
| Time to attain maximum concentration ($t_{max}$) | 4.50 h (2.00–7.00) |

* arithmetic mean

***Pharmacokinetics of Ritonavir***

| **General** | |
|---|---|
| **Absorption** | |
| Absolute bioavailability | Not known |
| Food effect | Food slightly decreases the bioavailability of ritonavir tablets.<br>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 protein binding *in vitro* | Approximately 98–99% and is constant over the concentration range of 1–100 µg/ml.<br>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.<br>Ritonavir penetrates minimally into the brain. |
| **Metabolism** | |
| | Primarily oxidative metabolism according to animal studies and *in vitro* experiments with human liver microsomes (HLMs).<br>Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite.<br>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 | 3-5 h |
| Mean systemic clearance (Cl/F) | 4.6 ± 1.6 L/h |
| % of dose excreted in urine | 11.3 ± 2.8% |
| % 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
copovidone
sodium chloride
sodium stearyl fumarate
sorbitan monolaurate

*Film coat*: colloidal anhydrous silica
hypromellose
hydroxypropyl cellulose
iron oxide yellow
polyethylene glycol
polysorbate 80

talc

titanium dioxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months.

### 6.4 Special precautions for storage

Do not store above 30°C. Store in original container.

### 6.5 Nature and contents of container

- White, plastic (HDPE) bottle with an opaque white cap with an inbuilt desiccant. Pack sizes: 30 tablets and 120 tablets.
- White, plastic (HDPE) bottle with an opaque white, plastic (polypropylene) screw closure and an aluminium induction sealing liner and a 1g silica gel desiccant canister. Pack sizes: 30 tablets.
- White, plastic (HDPE) bottle with an opaque white, plastic (polypropylene) screw closure and an aluminium induction sealing liner and a 2g silica gel desiccant canister. Pack sizes: 120 tablets.
- Aluminium foil blister card containing 10 tablets. One such blister is packed in a carton box.

### 6.6 Special precautions for disposal and other handling

No special requirements.

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

## 7. SUPPLIER

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Hyderabad – 500096, Telangana,

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## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA467

## 9. DATE OF PREQUALIFICATION

14 December 2010

## 10. DATE OF REVISION OF THE TEXT

November 2024

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*Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products*