# **Summary of Product Characteristics**

## **1 NAME OF THE MEDICINAL PRODUCT**

Ritonavir 100 mg film-coated tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablets contains 100 mg of ritonavir.

For the Full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

Film-coated tablet.

White to off white, capsule shaped, film-coated tablets, with a dimension of approx. 17.1 mm in length and 9.1 mm in width, debossed with 'H' on one side and 'R9' on other side.

#### **4 CLINICAL PARTICULARS**

#### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

Ritonavir should be administered by physicians who are experienced in the treatment of HIV infection. Ritonavir film-coated tablets are administered orally and should be ingested with food (see section 5.2). Ritonavir film-coated tablets should be swallowed whole and not chewed, broken or crushed.

Posology

Ritonavir dosed asa pharmacokineticenhancer

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

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

#### Adults:

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 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).

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Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in antiretroviral treatment (ART) experienced patients. Darunavir 800 mg once daily with ritonavir 100 mg once daily may be used in some ART experienced patients. Refer to the darunavir Summary of Product Characteristics for further information on once daily dosing in ART experienced patients.

Darunavir 800 mg once daily with ritonavir 100 mg once daily in ART-naïve patients

## Childrenandadolescents

Ritonavir is recommended for children 2 years of age and older. For further dosage recommendations, refer to the product information of other Protease Inhibitors approved for co-administration with ritonavir.

# Special populations

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

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

#### Ritonavir dosed as an antiretroviral agent Adults

The recommended dose of Ritonavir film-coated tablets is 600 mg (6 tablets) twice daily (total of 1200 mg per day) by mouth.

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

*Childrenandadolscents (2 years of age and above)*: The recommended dosage of ritonavir in children is 350 mg/m<sup>2</sup> by mouth twice daily and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m<sup>2</sup> and increased at 2 to 3 day intervals by 50 mg/m<sup>2</sup> twice daily (Other pharmaceutical forms/strengths may be more appropriate for administration to this population).

For older children it may be feasible to substitute tablets for the maintenance dose of the powder for oral suspension.

	oral suspension to tablets for emilaren
Powder for oral suspension dose	Tablet dose
176 mg (17.6 ml) twice daily	200 mg in the morning and 200 mg in the evening
262.5 mg (26.4 ml) twice daily	300 mg in the morning and 300 mg in the evening
350 mg (35.0 ml) twice daily	400 mg in the morning and 300 mg in the evening
438 mg (43.8 ml) twice daily	500 mg in the morning and 400 mg in the evening
526 mg (52.6 ml) twice daily	500 mg in the morning and 500 mg in the evening

# Dosage conversion from powder for oral suspension to tablets for children

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

# Special populations

#### Elderly

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

#### Renal impairment

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

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CRN00F7Y1

## Hepaticimpairment

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

## Paediatric population

The safety and efficacy of Ritonavir in childred aged below 2 years has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

# 4.3 Contraindications

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

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

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

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

The enzyme-modulating effect of ritonavir may be dose dependent. For some products, contraindications may be more relevant when ritonavir is used as an antiretroviral agent than when ritonavir is used as a pharmacokinetic enhancer (e.g. rifabutin and voriconazole):

Medicinal Product Class	Medicinal Products withinClass	Rationale
Concomitantmedicinal product levels increasedor 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,encain ide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole plasma concentrations and possible loss of effect (see section 4.5)

	. Health	Products Regulatory Authority
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with
And goot		renal and/or hepatic impairment (see sections 4.4 and 4.5).
Antihistamines	Astemizole,	Increased plasma concentrations of astemizole and terfenadine. Thereby,
,	terfenadine	increasing the risk of serious arrhythmias from these agents.
		Concomitant use of ritonavir (500 mg twice daily) dosed as an
		antiretroviral agent and rifabutin due to an increase of rifabutin serum
Antimycobacterial	Rifabutin	concentrations and risk of adverse reactions, including uveitis (see section
		4.4). Recommendations regarding use of ritonavir dosed as a
		pharmacokinetic enhancer with rifabutin are noted in section 4.5
	Lurasidone	Increased plasma concentrations of lurasidone which may increase the
		potential for serious and/or life-threatening reactions (see section 4.5).
Antipsychotics/Neuroleptics	Clozapine,	Increased plasma concentrations of clozapine and pimozide. Thereby,
	pimozide	increasing the risk of serious haematologic abnormalities, or other serious
		adverse effects from these agents.
	Questioning	Increased plasma concentrations of quetiapine which may lead to coma.
	Quetiapine	The concomitant administration with quetiapine is contraindicated (see
	Dihydroergotamine,	section 4.5).
	ergonovine,	Increased plasma concentrations of ergot derivatives leading to acute
Ergot Derivatives	ergotamine,	ergot toxicity, including vasospasm and ischaemia.
	methylergonovine	ergot toxicity, including vasospasin and ischaemia.
		Increased plasma concentrations of cisapride. Thereby, increasing the risk
GI motility agent	Cisapride	of serious arrhythmias from this agent
Lipid-modifying agents		Increased plasma concentrations of lovastatin and simvastatin, thereby,
HMG Co-A Reductase	Lovastatin,	increasing the risk of myopathy including rhabdomyolysis (see section
Inhibitors	simvastatin	4.5).
Microsomal triglyceride		
transfer protein (MTTP)	Lomitapide	Increased plasma concentrations of lomitapide (see section 4.5).
inhibitor		
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
		Contraindicated when used for the treatment of pulmonary arterial
		hypertension (PAH) only. Increased plasma concentrations of sildenafil.
	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).
	Clorazepate,	
	diazepam,	Increased plasma concentrations of clorazepate, diazepam, estazolam,
Sedatives/hypnotics	estazolam,	flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of
	flurazepam, oral	extreme sedation and respiratory depression from these agents. (For
	midazolam and	caution on parenterally administered midazolam, see section 4.5).
Ritonavir medicinal	triazolam	
product level decreased		
product level decreased		Herbal preparations containing St. John's wort ( <i>Hypericum perforatum</i> )
Herbal Preparation	St. John's Wort	due to the risk of decreased plasma concentrations and reduced clinical
		effects of ritonavir (see section 4.5).
	1	

# 4.4 Special warnings and precautions for use

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving ritonavir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.

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

## Patients with chronic diarrhoea or malabsorption

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

## Haemophilia

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

## Weight and metabolic parameters:

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

## Pancreatitis

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Ritonavir tablets therapy should be discontinued if a diagnosis of pancreatitis is made (see section 4.8).

## Immune Reconstitution Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

#### Liver disease

Ritonavir should not be given to patients with decompensated liver disease (see section 4.2).Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

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

#### Renal disease

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

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

Osteonecrosis: Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced

HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

## PR interval prolongation

Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicinal products known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. Ritonavir tablets should be used with caution in such patients (see section 5.1).

## Interactions with other medicinal products

Ritonavir dosed as an antiretroviral agent

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

## PDE5 inhibitors

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

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

## HMG-CoA reductase inhibitors

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

#### Colchicine

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

# Digoxin

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

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

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

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

### Trazodone

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

## Rivaroxaban

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

## Riociguat

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

## Vorapaxar

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

## Bedaquiline

Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co- administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline Summary of Product Characteristics).

## Delamanid

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

# Ritonavir dosed as a pharmacokinetic enhancer

The interaction profiles of HIV-protease inhibitors, co-administered with low dose ritonavir, are dependent on the specific co-administered protease inhibitor.

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

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

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

#### Fosamprenavir

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

#### Atazanavir

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

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

## 4.5 Interaction with other medicinal products and other forms of interaction

## Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

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

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

## Medicinal products that affect ritonavir levels

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

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

# Medicinal products that are affected by the use ofritonavir

Interactions between ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in the tables below. This list is not intended to be inclusive or comprehensive. Individual SmPCs should be consulted.

Co- Administered Medicinal Product	Dose of Co- administ ered Medicinal Product (mg)	D so R o av (r g	e f it n ir n	Medic inal Produ ct Assess ed	AUC		C <sub>min</sub>	
Amprenavir	600 q12h	10 q1 21		Ampre navir <sup>1</sup>	↑ 64%		↑5 fold	

#### **Medicinal Product Interactions – Ritonavir with Protease inhibitors**

		Health Prod	ucts R	egulat	ory A	uthority	 			
	Ritonavir									
	increases									
	the									
	serum									
	levels of									
	amprena vir as a									
	result of									
	CYP3A4									
	inhibition.									
	Clinical									
	trials									
	confirmed									
	the									
	safety									
	and									
	efficacy									
	of 600									
	mg									
	amprena									
	vir twice									
	daily with									
	ritonavir									
	100 mg									
	twice									
	daily. For									
	further									
	informati									
	on,									
	physicians									
	should									
	refer to									
	the									
	Summary									
	of Product									
	Character									
	istics for									
	amprena									
	vir.									
	VII.					Atazan			↑ 11	
			100			avir	1 86%		fold	
Atazanavir	300 q24h		q2			Atazan	↑2		↑ 3-7	
			4h			avir <sup>2</sup>	fold		fold	
	Ritonavir									
	increases									
	the									
	serum									
	levels of									
	atazanavir									
	as a									
	result of									
	CYP3A4									
	inhibition.									
	Clinical									
	trials									
	confirmed									
	the									
	safety									
	and									

-		Health Proc	lucts R	egulat	ory A	uthority	-	•	-	 
	efficacy									
	of 300									
	mg .									
	atazanavir									
	once									
	daily with									
	ritonavir									
	100 mg									
	once									
	daily in									
	treatment									
	lieaunent									
	experienc									
	ed									
	patients.									
	For									
	further									
	informati									
	on,									
	physicians									
	should									
	refer to									
	the									
	Summary									
	of									
	Product									
	Character									
	istics for									
	atazanavi									
1										
	r		100							
	r		100			Darun	↑ 1 <i>A</i>			
Darunavir	r 600,					Darun	↑ 14			
Darunavir	r		q1			Darun avir	↑ 14 fold			
Darunavir	r 600, single									
Darunavir	r 600, single Ritonavir		q1							
Darunavir	r 600, single Ritonavir increases		q1							
Darunavir	r 600, single Ritonavir		q1							
Darunavir	r 600, single Ritonavir increases the		q1							
Darunavir	r 600, single Ritonavir increases the serum		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition.		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect.		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher than 100		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher than 100 mg twice		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher than 100 mg twice daily		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher than 100 mg twice		q1							
Darunavir	r 600, single Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeut ic effect. Ritonavir doses higher than 100 mg twice daily		q1							

		Health Proc	lucts R	egulat	tory A	uthority	-				
	studied										
	with										
	darunavir.										
	For										
	further										
	informati										
	on, refer										
	to the										
	Summary of										
	Product										
	Character										
	istics for										
	darunavir	 									$\square$
Fosamprena			100			Ampre		12.4		↑ 11	
vir	700 q12h		q1			navir		fold		fold	
VII			2h			navn		1010		ioid	
	Ritonavir										
	increases										
	the										
	serum										
	levels of										
	amprena										
	vir (from										
	fosampre										
	navir) as										
	a result										
	of										
	CYP3A4										
	inhibition.										
	Fosampr										
	enavir										
	must be										
	given										
	with										
	ritonavir										
	to ensure										
	its										
	therapeut										
	ic effect.										
	Clinical										
	trials										
	confirmed										
	the										
	safety										
	and										
	efficacy										
	of										
	fosampre										
	navir 700										
	mg twice										
	daily with										
	ritonavir										
	100 mg										
	twice										
	daily.										
	Ritonavir										
	doses										
	higher										
	than 100										

		Health Proc	ucts R	egula	tory A	uthority	1		1		
	mg twice										
	daily										
	have not										
	been										
	studied										
	with										
	fosampre										
	navir. For										
	further										
	informati										
	on,										
	physicians										
	should										
	refer to										
	the										
	Summary										
	of										
	ProductC										
	haracteris										
	tics for										
	fosampre										
	navir										
			100								
Indinavir	800 q12h		q1			Indina		178% ↑		ND	
	000 9.2		2h			vir <sup>3</sup>					
			211			Ritona					
						vir		↑ 72%		ND	
			400								
	400 a12b					Indina				↑4	
	400 q12h		q1			vir <sup>3</sup>		$\leftrightarrow$		fold	
			2h								
						Ritona		$\leftrightarrow$		$\leftrightarrow$	
						vir					$\square$
	Ritonavir										
	increases										
	the										
	serum										
	levels of										
	indinavir										
	as a										
	result of										
	CYP3A4										
	inhibition.										
	Appropri										
	ate doses										
	for this										
	combinat										
	ion, with										
	respect										
	to										
	efficacy										
	and										
	safety,										
	have not										
	been										
	establish										
	ed.										
	Minimal										
	benefit of										
	ritonavir-										
									 		<u> </u>

		Health Prod	ucts R	egulat	ory A	uthority					
	mediated										
	pharmac										
	okinetic										
	enhance										
	ment is										
	achieved										
	with										
	doses										
	higher										
	than 100										
	mg twice										
	daily. In										
	cases of										
	co-admin										
	istration										
	of										
	ritonavir										
	(100 mg										
	twice										
	daily) and										
	indinavir										
	(800 mg										
	twice										
	daily)										
	caution is										
	warranted										
	as the										
	risk of										
	nephrolit										
	hiasis										
	may be										
	increased.										
	increased.										
			100					A 20			
	1250		100			Nelfin		↑20			
Nelfinavir	q12h		q1			avir		to		ND	
	9.=		2h					39%			
			500			Nelfin					
	750,					avir		152% ↑		ND	
	single		q1			Ritona		$\leftrightarrow$		$\leftrightarrow$	
			2h			vir					
	Ritonavir										
	increases										
	1										
	the										
	serum										
	levels of										
	nelfinavir										
	as a										
	result of										
	CYP3A4										
	inhibition.										
	Appropri										
	ate doses										
	for this										
	combinat										
	ion, with										
	respect										
	to										
	efficacy										
	and										
	safety,										
04 April 2024							Dago 12				<b>—</b> І

		Health Proc	ducts R	egulat	tory A	uthority				-	
	have not										
	been										
	establish										
	ed.										
	Minimal										
	benefit of										
	ritonavir-										
	mediated										
	pharmac										
	okinetic										
	enhance										
	ment is										
	achieved										
	with										
	doses										
	higher										
	than 100										
	mg twice										
	daily.										
						Saquin					
	1000		100			avir <sup>4</sup>		15-f		15-fo	
Saquinavir			q1					old		ld	
	q12h		2h			Ritona		$\leftrightarrow$		$\leftrightarrow$	
						vir					$\square$
			400			Saquin		17-f			
	400 q12h		q1			avir <sup>4</sup>		old		ND	
	400 91211		2h			Ritona		↔		$\leftrightarrow$	
			211			vir					
	Ritonavir										
	increases										
	the										
	serum										
	levels of										
	saquinavir										
	as a										
	result of										
	CYP3A4										
	inhibition.										
	Saquinavir										
	should										
	only be										
	given in										
	combinat										
	ion with										
	ritonavir.										
	Ritonavir										
	100 mg										
	twice										
	daily with										
	saquinavir										
	1000 mg										
	twice										
	daily										
	provides										
	saquinavir										
	systemic										
	exposure										
	over 24										
	hours										
	similar to										
	or										
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		Health Prod	ucis R	egulai	Ory A	uthonty				 
	greater									
	than									
	those									
	achieved									
	with									
	saquinavir									
	1200 mg									
	three									
	times									
	daily									
	without									
	ritonavir.									
	ln a									
	ln a									
	clinical									
	study									
	investigat									
	ing the									
	interaction									
	of									
	rifampicin									
	600 mg									
	once									
	daily and									
	saquinavir									
	1000 mg									
	with									
	ritonavir									
	100 mg									
	twice									
	daily in									
	healthy									
	volunteer									
	s, severe									
	hepatoce									
	llular									
	toxicity									
	with									
	transami									
	nase									
	elevations									
	up to >									
	20-fold									
	the upper									
	limit of									
	normal									
	after 1 to									
	5 days of									
	co-admin									
	istration									
	was									
	noted.									
	Due to									
	the risk									
	of severe									
	hepatoxic									
	ity,									
	saquinavi									
	r/ritonavir									
	should									
0024	Should						Dago 15	<u> </u>		

		Health Proc	iucts r	egula	tory P	uthonty						
	not be											
	given											
	together											
	with											
	rifampici											
	n.											
	For											
	further											
	informati											
	on,											
	physicians											
	should											
	refer to											
	the											
	Summary											
	of											
	Product											
	Character											
	istics for											
	saquinavi											
	r											
			200				1		1		1	$\square$
Tiproposit	E00 ~12b					Tipran		111			129	
Tipranavir	500 q12h		q1			avir		fold			fold	
			2h									
						Ritona		1400/				
						vir		↓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											
	therapeut											
	ic effect.											
	Doses of											
	ritonavir											
	less than											
	200 mg											
	twice											
	daily											
	should											
	not be											
	used with											
	tipranavir											
	as they											
	might											
	alter the											
	efficacy											
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 	 Health Proc	ucts R	egulat	ory A	uthonty		 	 
of the								
combinat								
ion. For								
further								
informati								
on,								
physicians								
should								
refer to								
the								
Summary								
of								
Product								
Character								
istics for								
tipranavir								
								 -
ND: Not								
determin								
ed.								
1. Based								
on								
cross-stu								
dy								
comparis								
on to								
1200 mg								
amprena								
vir twice								
daily								
alone.								
2. Based								
on								
cross-stu								
dy								
comparis								
on to 400								
mg								
atazanavir								
once								
daily								
alone.								
3. Based								
on								
cross-stu								
dy								
comparis								
on to 800								
mg								
indinavir								
three								
times								
daily								
alone.								
4. Based								
on								
cross-stu								
dy								
comparis								
on to 600								
mg								
9								

			Health Prod	ucts Re	gulatory A	uthority					
	saquinavir three times daily alone.										
Medicinal Pro	duct Intera	ctions – Ritonav	ir with Antir		al Agents	Other Th	an Prote	ase inhi	bitors	1	
Co- Administered Medicinal Product	Dose of Co- administ ered Medicinal Product (mg)			Do se of Rit on avir (m g)		Medic inal Produ ct Assess ed		AUC			C <sub>min</sub>
Didanosine	200 q12h			600 q1 2h 2 h late r		Didan osine		↓13%			¢
	As ritonavir is recomme nded 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 necessar y.										
Delavirdine	400 q8h			600 q1 2h		Delavi rdine <sup>1</sup>		$\leftrightarrow$			$\leftrightarrow$
	Based on comparis on to historical data, the pharmac okinetics					Ritona vir		↑ 50%			↑75%

		Health Prod	iucts R	egulat	.ory A	uthority			1			
	of delavirdi ne did not appear to be affected by ritonavir. When used in combinat ion with delavirdi ne, dose reduction of ritonavir may be considere d.											
Efavirenz	600 q24h		500 q1 2h			Efavire nz		↑ 21%				
						Ritona vir		17% ↑				
	A higher frequency of adverse reactions (eg, dizziness, nausea, paraesth esia) and laboratory abnormal ities (elevated liver enzymes) have been observed when efavirenz is co-admin istered with ritonavir dosed as an antiretrov iral agent.											
Maraviroc	100 q12h		100 q1 2h			Maravi roc		↑ 161%			↑ 28%	
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		1	Health Proc	lucts R	egulat	ory A	uthority					
	Ritonavir											
	increases											
	the											
	serum											
	levels of											
	maraviroc											
	as a											
	result of											
	CYP3A											
	inhibition.											
	Maraviroc											
	may be											
	given											
	with											
	ritonavir											
	to											
	increase											
	the											
	maraviroc											
	maraviroc											
	exposure.											
	For											
	further											
	informati											
	on, refer											
	to the											
	Summary											
	of											
	Product											
	Character											
	istics for											
	maraviro											
	с.											
				600								
Nevirapine	200 q12h			q1			Nevira	$\leftrightarrow$			$\leftrightarrow$	
liternapine	200 91211			2h			pine					
				211			Ritona					
								$\leftrightarrow$			$\leftrightarrow$	
							vir					
	Co-admi											
	nistration											
	of											
	ritonavir											
	with											
	nevirapine											
	does not											
	lead to											
	clinically											
	relevant											
	changes											
	in the											
	pharmac											
	okinetics											
	of either											
	nevirapine											
	or											
	ritonavir.			100				 				$\vdash$
Dalta -	400			100			Ralteg	1.1.00			1.40/	
Raltegravir	single			q1 2h			ravir	↓ 16%			↓1%	
		•	1	i Jh				1	1	1		i

	-		Health Proc	lucts R	legula	tory A	uthority				
	Co-admi nistration										
	of ritonavir										
	and										
	Raltegrav										
	ir results										
	in a										
	minor										
	reduction										
	in										
	Raltegrav										
	ir levels.			300			Zidov				
Zidovudine	200 q8h			900 q6h			udine	↓ 25%		ND	
	Ritonavir										
	may										
	induce										
	the										
	glucuroni										
	dation of zidovudin										
	e, resulting										
	in slightly										
	decreased										
	levels of										
	zidovudin										
	e. Dose										
	alterations										
	should										
	not be										
	necessar										
	у.										
	ND: Not										
	determin										
	ed 1.Based										
	on on										
	parallel										
	group										
	comparis										
	on.										
Ditonovir offe	ets on Nor	antiretroviral Co	o-administer		dicir	al P**					
							Effect		Effect		$\square$
					Do		on		on		
		Dose of			se		Coad		Coad		
Co-administ		Coadminister			of		minist		minist		
ered		ed			Rit		ered		ered		
Medicinal		Medicinal			on avi		Medic		Medic		
Products		Products			r		inal		inal		
		(mg)			(m		Produ		Produ		
					g)		cts		cts		
					<i>,</i> ,		AUC		C <sub>max</sub>		$\parallel$
Alpha1-Adr											
enoreceptor Antagonist											
Alfuzosin		Ritonavir									$\square$
	•						•	-		-	

·			Health Prod	ucts R	egulat	ory A	uthority				
Amphetami ne Derivatives	tion to re incre plas cone of a and ther <b>trai</b> (see 4.3).	centrations alfuzosin is refore <b>con</b> <b>ndicated</b> section	Health Prod	ucts R	egulat	ory A	uthority				
Amphetamin e	antin agen to ir CYP as a expe incre cone of amp and deri Care mor ther and effe reco whe med cone adm with antin dose ritor	retroviral nt is likely hibit 2D6 and result is ected to ease centrations ohetamine its vatives. eful hitoring of rapeutic adverse cts is ommended en these dicines are comitantly hinistered									
Analgesics											$\square$
Buprenorphi ne Norbuprenor phine Glucuronide metabolites	16 c	124h			100 q1 2h		157% 133% ↔		↑ 77% ↑108% ↔		
	of p leve bup and met did	increases lasma ls of renorphine l its active abolite not lead linically									

		Health Proc	lucts R	egulat	ory A	uthority	 	 	 
	significant								
	pharmacodyn								
	amic 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								
	buprenorphin								
	e, the								
	Summary of								
	Product								
	Characteristics								
	of the								
	co-administer								
	ed protease								
	inhibitor								
	should be								
	reviewed for								
	specific								
	dosing								
	information.								
	Ritonavir								
	co-administra								
	tion is likely								
	to result in								
	increased								
	plasma								
	concentrations								
Pethidine,	of								
piroxicam,									
propoxyphe	norpethidine,								
ne	piroxicam,								
	and								
	propoxyphene								
	and is								
	therefore <b>con</b>								
	traindicated								
	(see section								
	4.3).								
	Ritonavir								
	dosed as a								
Fentany <sup>l</sup>	pharmacokine								
	tic enhancer								
							 (70		

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		
agent inhibits       agent inhibits         CYP3A4 and       as a result is         expected to       as a result is         increase the       as a result is         plasma       as a result is         concentrations       as of fentanyl.         Careful       as a result is         monitoring of       as a result is		
CYP3A4 and       as a result is         as a result is       expected to         increase the       increase the         plasma       increase the         concentrations       increase         of fentanyl.       Careful         monitoring of       increase         therapeutic       increase		
CYP3A4 and       as a result is         as a result is       expected to         increase the       increase the         plasma       increase the         concentrations       increase         of fentanyl.       increase         Careful       increase         monitoring of       increase         therapeutic       increase		
expected to       increase the         plasma       increase in the         concentrations       increase         of fentanyl.       increase         Careful       increase         monitoring of       increase         therapeutic       increase		
increase the       increase the <td< td=""><td></td><td></td></td<>		
increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic		
concentrations of fentanyl. Careful monitoring of therapeutic		
of fentanyl. Careful monitoring of therapeutic		
Careful monitoring of therapeutic		
monitoring of therapeutic		1
therapeutic		
and adverse	I	
effects		
(including		
respiratory		
depression) is		
recommended		
when		
fentanyl is		
concomitantly		
administered		
with ritonavir.		+
500		
Methadone <sup>1</sup> 5, single doseq1 $\downarrow 36\%$ $\downarrow 38\%$		
Increased		Т
methadone		
dose may be		
necessary		
when when		
concomitantly		
administered		
with ritonavir		
dosed as an		
antiretroviral		
agent or as a		
pharmacokine		
tic enhancer		
due to		
induction of		
glucuronidati		
on. Dose		
adjustment		
should be		
considered       based on the		
patient's		
response to		
methadone		
therapy.		
Morphine		t
Morphine levels may be		
decreased		
due to		
Antianginal     induction of       Ranolazine     induction of		
glucuronidati glucuronidati		

	 	Health Proc	iucts R	egula	tory A	uthority			i	 	
	on by										
	co-administer										
	ed ritonavir										
	dosed as an										
	antiretroviral										
	agent or as a										
	pharmacokine										
	tic enhancer.										
	Due to CYP3A										
	inhibition by										
	ritonavir,										
	concentrations										
	of ranolazine										
	are expected										
	to increase.										
	The										
	concomitant										
	administration										
	with										
	ranolazine is										
	contraindicated	4									
	(see section										
	4.3).										
Antiarrthym											$\vdash$
ics											
	Ritonavir										
	co-administra										
	tion is likely										
	to result in										
	increased										
	plasma										
	concentrations										
Amiodarone,	of										
bepridil,											
dronedarone,	amiodarone,										
encainide,	bepridil,										
flecainide,	dronedarone,										
propafenone,	encainide,										
quinidine	flecainide,										
quintante	propafenone,										
	and quinidine										
	and is										
	therefore <b>con</b>										
	traindicated										
	(see section										
	4.3).										
				300							
	0.5 single IV			q1							
Digoxin	dose			2h,		1 86%			ND		
				3							
				da							
				ys							
				200							
	0.4 single oral			q1		↑ 22%			$\leftrightarrow$		
	dose			2h,		1 <u>2</u> 2 /0					
				13							
	 			da							
044 10004							D 05	( 70		 	_

			Health Prod	UCIS R		lory P	uthonty	 r				
					ys							$\square$
		This										
		interaction										
		may be due										
		to										
		modification										
		of										
		P-glycoprotein										
		mediated										
		digoxin efflux										
		by ritonavir										
		dosed as an										
		antriretroviral										
		agent or as a										
		pharmacokine										
		tic enhancer.										
		Increased										
		digoxin levels										
		observed in										
		patients										
		receiving										
		ritonavir may										
		lessen over										
		time as										
		induction										
		develops (see										
		section 4.4).										
Antiasthmat		3ECUUII 4.4).										$\left  \right $
ic												
					500							
					500							
Theophylline		3 mg/kg q8h					↓43%		↓32%			
		5, 5 1			q1							
					2h							
		An increased										
		dose of										
		theophyline										
		may be										
		required										
		when										
		coadministered										
		with ritonavir,										
		due to										
		induction of										
		CYP1A2.										
Anticancer												$\vdash$
agents and												
kinase												
inhibitors												
											L	$\left  \right $
Afatinib		20 ma single										
		20 mg, single										
		200 q12h/1h										
		↑ 48% ↑ 39%										
		dose before										
		40 mg, single										
		200 q12h/ co										
		↑ 19% ↑ 4%										
		Dose										
		administered										
		40 mg, single										
	•				•					•		-

200 q12h/6h 111% 15% Does after     1       Abemacidib     Serum concentrations may be increased due to Broast     1       Abemacidib     to Broast       Apalutamide     P-0p increase in and acute       Apalutamide     P-0p intribution by introase in AUC and       Certinib     Cmax depends on the triining of introase administratio       Dasatinib, informari administratio     AUC and       Dasatinib, informari administratio     Informari administratio       Becorafenib     Encorafenib       Ibrutinib     Concentrations may of product       Festamatinib     Serum administration informari, concentrations may be increased due to CYSA4 inhibition by ritonari, should be avoided. If this co- unavoidable, and ritonavir is judged unavoidable, administration is judged unavoidable, administration is judged unavoidable, administration is judged unavoidable, administration is judged	i i		h Products Regulato	ry Authority	-ii	
Dose after		200 q12h/6h				
Abemaciclib Serum concentrations may be increased due to Breast Carrene Resistance Protein (BCRP) and acute Protein (BCRP) and acute and acute protein (BCRP) and acute and acute and atomavie and atomavie		↑ 11% ↑ 5%				
Abemacidib		Dose after				
Abemacidib						
Abemaciclib increased due to Breast Cancer Resistance Protein (SCR9) and acute Page increase in a cut of increase		Serum				
Abemacidib increased lue cancer Resistance Protein (BCRP) and acute Pro		concentrations				
Abemacicilio concor Resistance Protein (BCRP) and acute Apalutamide P-gp inhibition by ritonavir. The extent of increase in AUC and Certinib Conax depends on the timing of ritonavir administratio Dasatinib, n. Caution infolnib, should be vincristine, Ceractristic Fostamatinib Binomary of Product Createristic Fostamatinib Ner		may be				
Apalutamide       Carcer Resistance Protein (BCRP) and acute P-gp inhibition by ritonawir. The extent of increase in AUC and Certinib       P-gp inhibition by ritonawir.         Certinib       Cmix         AUC and Comax       Cmix         AUC and Comax       Cmix         AUC and Comax       Cmix         AUC and Comax       Cmix         Dasatinib, niconavir administratio       Caution nitonavir administratio         Dasatinib, vincristine, vincristine, corrafemb       Caution conservice afainib         Encorafemb       (refer to the afainib         Summary of Product       Characteristic S). Monitor for ADR related to afatinib.         Ibrutinib       Serum ronavir, co-administra         Neratinib       Serum ronavir, co-administra         Neratinib       Serum ronavir, co-administra         Neratinib       Serum ronavir, co-administra         Neratinib       Serum ronavir, co-administra         Venetoclax       Biodebio administration administratio		increased due				
Apalutamide       Resistance Protein (BCRP) and acute       P-gp         Apalutamide       P-gp         inhibition by ritonawir. The extern of increase in AUC and Certinib       AUC and Camax         Certinib       Cmax depends on the timing of ritonawir administratio       Image: Comax depends on the timing of ritonawir administratio         Dasatnib, nilotinib, wincristine, vincristine, externation       n. Caution       Image: Comax depends on the timing of ritonawir administratio         Dasatnib, milotinib, vincristine, vincristine, externation       n. Caution       Image: Comax depends on the timing of ritonawir administratio         Brould be vincristine, vincristine, fostamatinib       Serum Concentrations may be increased due to CY93A4 inhibition by ritonavir, should be avoided. If this co- administration is should be avoided. If this co- administration is should be avoided. If this co- administration is judged unavoidable, refer to the abemacicib SmPC for dosage       Image: Comax depends on the time of this co- administration	Abemaciclib	to Breast				
Apalutamide       Protein (BCRP) and acute Progo inhibition by rincoavir. The extent of increase in AUC and Ceritinib       AuC and Camax       Image: Comparison of the depends on the timing of rincoavir. administratio         Dasatinib, nilotinob, vincristine, vincristine, source and vincristine to cortanib       Ceritinib       Image: Comparison of the depends on the timing of rincoavir. administratio       Image: Comparison of the depends on the timing of rincoavir. administratio       Image: Comparison of the depends on the timing of rincoavir.         Dasatinib, vincristine, vincristine, source and vincristine to cortanib       Image: Comparison of the depends on the timing of rincoavir.       Image: Comparison of the depends on the timing of rincoavir.         Fostamatinib       Serum concentrations may be increased due to of pade abemacicib abemacicib administratio       Image: Comparison of the depends on the timing of rincoavir.       Image: Comparison of the depends on the timing of rincoavir.         Neratinib       Serum concentrations may be avoided. If this co- administration administrati		Cancer				
Apalutamide       and acute       and acute         Apalutamide       "Popp"         inhibition by       ritonavir. The         autorawir       autorawir         AUC and       autorawir         depends on       autorawir         depends on       autorisitatio         Dasatnilb,       n. Caution         nilotinib,       n. Caution         Ninblatine       administration         Broduct       Commany of         Product       Concentrations         may be       increased due         to of       abemacilib         abemacilib       administration         should be       administration         should be       administration		Resistance				
Apalutamide       P-gp inhibition by inhibition by increase in AUC and       Image: second se		Protein (BCRP)				
Inibition by       initiation by         extent of       increase in         AUC and       increase in         AUC and       increase in         administratio       increase in         Dasatinib,       n. Caution         infointin,       should be         vincristine,       exercised in         vincristine,       exercised in         vincristine,       exercised in         Vinblastine       administering         afatinib       afatinib         Ritonavir       manual         Product       Characteristic         Summary of       Product         Product       Concentrations         may be       increased due         to CrYP3A4       initiotion         initiotion of       abemacicib         administration       in of         abemacicib       administration         tion of       abemacicib         administration       in of         abemacicib       administration         should be       administration         tion of       abemacicib         abemacicib       administration         administration       in of         abemacici		and acute				
Ceritinib       ritonavir. The extent of increase in AUC and Cepends on the timing of ritonavir administratio         Dasatinib,       n. Caution         Dasatinib,       n. Caution         nilotnib,       should be vincristing affainib         Vinolistine       administering affainib         Bitonavir       administering affainib         Summary of Product       Product         Postamatinib       Summary of Product         Postamatinib       Serum         Concentrations       Serum         Ibrutinib       Serum         Concentrations       concentrations         may be       increased due to CY93A4         inhibition by       ritonavir         should be abemacicilib       administration         administration       abemacicilib         abemacicilib       abemacicilib         abemacicilib       abemacicilib         abemacicilib	Apalutamide	P-gp				
Ceritinib       extent of increase in AUC and Cana Construction of the timing of ritonavir administratio         Dasatinib, n. Caution nilotinib, should be exercised in vincristine, exercised in Vinblastine administratio       exercised in Vinblastine Construction of the timing of ritonavir administration of the time of time of time of time of time of time of the time of t						
Certinib       Increase in AUC and depends on the timing of ritonavir administratio         Dasatinib, nilotinib, wincristne, wincri						
Ceritinib       AUC and Cmax       Cmax         Qendo on the timing of ritonavir administratio       administratio         Dasatinib, initotinib, vincristine,       exercised in         wincristine,       exercised in         afatinib with afatinib with afatinib       Ritonavir         Encorafenib       (refer to the afatinib         Broduct       Product         Fostamatinib       Summary of Product         Fostamatinib       Serum concentrations may be increased due to afatinib.         Ibrutinib       Serum concentrations may be increased due to cr93A4 inhibition by ritonavir. Co-administra         Neratinib       tion of abemacicib and mitonavir should be administration is judged unavoidable, refer to the abemacicib SmPC for						
Ceritinib       Cmax depends on the timing of ritonavir administratio       Image: Construction of the timing of ritonavir administratio       Image: Construction of time o						
depends on the timing of the timing of administratio       administratio       administratio         Dasatinib,       n. Caution       i       i       i       i       i         nilotinib,       should be       i<						
Neratinib       Serum         Co-administratio       Serum         Ibrutinib       Serum         Concentrations       Serum         Concentrations       Serum         Serum       Concentrations         Ibrutinib       Serum         Concentrations       Serum         Concentrations       Serum         Serum       Serum         Concentrations       Serum         Serum       Serum         Serum       Serum         Serum       Serum         Serum       Serum         Concentrations       Serum         Serum       Serum         Serum       Serum         Serum       Serum         Serum       Serum         Condentistration       Serum         Serum       Serum<	Ceritinib					
Dasatinib, nilotinib, vincristine, vincristine, vincristine, exercised in administering afatinib with Ritonavir Encorafenib       administering afatinib with Ritonavir exercised in vinbistine       administering afatinib with Ritonavir         Encorafenib       (refer to the afatinib Summary of Product       administering afatinib       administering afatinib         Encorafenib       Serum concentrations may be increased due to C4P3A4 inhibition by ritonavir.       Serum concentrations may be increased due to C4P3A4 inhibition by ritonavir.       Image: Serum concentrations is judged unavoidable, refer to the abemaciclib SmPC for       Image: Serum concentrations is judged unavoidable, refer to the abemaciclib       Image: Serum concentrations is judged unavoidable, refer to the abemaciclib       Image: Serum concentrations is judged unavoidable, refer to the abemaciclib       Image: Serum concentrations is judged unavoidable, refer to the abem		-				
Dasatinib,       administratio         Dasatinib,       n. Caution         nilotinib,       should be         vincristine,       exercised in         administering       administering         administering       administering         administering       administering         administering       administering         administering       administering         administering       administering         afatinib with       Ritonavir         Encorafenib       (refer to the         afatinib       Summary of         Product       Characteristic         Fostamatinib       Serum         concentrations       may be         increased due       to afarib.         librutinib       Serum         concentrations       may be         increased due       to CorParations         may be       increased due         increased due       to or of         administration       administration         administration       administration         is judged       administration         unavoidable,       refer to the         abemaci(lib       administration         is judged						
Dasatinib, nilotinb, vincristine, Vinblastine       n. Caution       n. Caution       n. Caution         wincristine, vincristine, vincristine, exercised in vincristine, exercised in vincristine, exercised in vincristine, exercised in vincristine, exercised cue to afarinib.       administering afatinib with afatinib summary of Product       administering afatinib summary of Product       administering afatinib summary of Product         Fostamatinib       Sexum concentrations may be increased due to afarinib.       sexum concentrations may be increased due to CYP3A4 inhibition by ritonavir.       sexum concentrations may be increased due to CYP3A4 inhibition by ritonavir.       sexum concentrations may be increased due to Co-administra tion of abemaciclib and ritonavir should be unavoidable, refer to the abemaciclib abemaciclib smPC for       sexum concentrations may be increased due to Co-administra tion of abemaciclib and ritonavir should be unavoidable, refer to the abemaciclib abemaciclib abemaciclib       sexum concentration is judged unavoidable, refer to the abemaciclib abemaciclib       sexum concentration is judged unavoidable, refer to the abemaciclib       sexum concentration is judged unavoidable, refer to the abemaciclib <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
nilotinib, exercised in exercised in administrating afatinib with Ritonavir (refer to the afatinib Summary of Product Characteristic S). Monitor for ADRs related to afatinib.						
vincristine, exercised in administering administering administering afatinib with Ritonavir Encorafenib (refer to the afatinib Summary of Product Characteristic S). Monitor for ADRs related to afatinib. Fostamatinib S. Summary of uncertainty of the second state of t						
Vinblastine       administering afatinib with Ritonavir       administering afatinib with Ritonavir         Encorafenib       (refer to the afatinib       afatinib         Summary of Product       Product         ADRs related to afatinib.       ADRs related to afatinib.       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.         Neratinib       Co-administra tion of abemaciclib and ritonavir should be avoided. If this co- unavoidable, refer to the abemaciclib SmPC for       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.         Venetoclax       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.         Venetoclax       Image: Concentration is judged unavoidable, refer to the abemaciclib SmPC for       Image: Concentration is judged unavoidable, refer to the abemaciclib       Image: Concentration is judged unavoidable, refer to the abemacic						
Encorafenib in the second seco						
Encorafenib       Ritonavir       Image: constraint of the straint of the str	Vinblastine					
Encorafenib (refer to the afatinib Summary of Product Characteristic s). Monitor for ADRs related to afatinib. Postamatinib Serum Concentrations may be increased due to CYP3A4 inhibition by ritonavir. Neratinib tion of abemaciclib and ritonavir should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage						
afatinib       Summary of         Product       Characteristic         S) Monitor for       ADRs related         ADRs related       to afatinib.         Ibrutinib       Serum         concentrations       may be         increased due       to CYP3A4         inhibition by       ritonavir.         Co-administra       Co-administra         tion of       abemaciclib         administration       is judged         unavoidable,       refer to the         abemaciclib       Sministration         is judged       unavoidable,         refer to the       abemaciclib         should be       avoidable,	En constantin					
Fostamatinib       Summary of Product Characteristic S. Monitor for ADRs related to afatinib.       Image: Concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Concentrations may be abemaciclib SmPC for dosage       Image: Concentration may be increased due to Concentration is judged inavoidable, refer to the abemaciclib SmPC for       Image: Concentration may be increased due to Concentration may be increased due	Encoratenio					
Fostamatinib       Product Characteristic s). Monitor for ADRs related to afatinib.       Serum         Ibrutinib       Serum concentrations may be increased due to CVP3A4 inhibition by ritonavir.       Image: Concentration of abemaciclib and ritonavir should be avoided. If       Image: Concentration of abemaciclib and ritonavir should be avoided. If         Venetoclax       this con- is judged unavoidable, refer to the abemaciclib SmPC for       Image: Concentration of abemaciclib and ritonavir should be       Image: Concentration of abemaciclib and ritonavir should be						
Fostamatinib       Characteristic         Solution for         ADRs related         to afatinib.         Brutinib         Serum         concentrations         may be         increased due         to CVP3A4         inhibition by         ritonavir.         Co-administration         abemaciclib         and ritonavir         should be         avoided. If         this co-         administration         is judged         unavoidable,         refer to the         abemaciclib         same         administration         is judged         unavoidable,         refer to the         abemaciclib         smedicibi         administration         is judged         unavoidable,         refer to the         abemaciclibi         smedicibi         smedicibi         smedicibi         smedicibi         smedicibi         smedicibi         smedicibi         smedicibi         smedicibi						
Fostamatinib       s). Monitor for ADRs related to afatinib.       Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       Serum concentrations       Image: Serue serue concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Serue concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       Image: Serue to Serue to CP       Image: Serue to Serue to CP       Image: Serue to CP						
ADRs related to afatinib.       Serum         Ibrutinib       Serum         concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Concentrations Concentrations         Neratinib       Co-administra         Neratinib       tion of abemaciclib and ritonavir should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       Image: Concentration is in this contract on the this conthis	Fostamatinih					
Ibrutinib       Serum         Ibrutinib       Serum         concentrations       may be         increased due       to CYP3A4         inhibition by       ritonavir.         Co-administra       Co-administra         tion of       abemaciclib         and ritonavir       should be         avoided. If       this co-         venetoclax       administration         is judged       unavoidable,         refer to the       abemaciclib         SmPC for       dosage						
Ibrutinib       Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir.       Image: Concentrations may be increased due to CYP3A4       Image: Concentrations may be increased due to CYP3A4         Neratinib       Co-administra       Image: Concentrations intono of abemaciclib and ritonavir should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       Image: Concentrations intonavir       Image: Concentrations is judged intonavir						
Ibrutinib Ibruti						
Neratinib       may be increased due to CYP3A4 inhibition by ritonavir.       inhibition by ritonavir.       inhibition by ritonavir.       inhibition by ritonavir.         Co-administra       inhibition of abemaciclib and ritonavir should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       inhibition by ritonavir       inhibition by ritonavir		Serum				
Neratinib       may be increased due to CYP3A4 inhibition by ritonavir.       inhibition by ritonavir.       inhibition by ritonavir.       inhibition by ritonavir.         Co-administra       inhibition of abemaciclib and ritonavir should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       inhibition by ritonavir       inhibition by ritonavir	Ibrutinib					
Neratinib       increased due       inhibition by         ritonavir.       Co-administra         Co-administra       inhibition by         tion of       abemaciclib         and ritonavir       inhibition by         should be       inhibiton         avoided. If       inhibiton         this co-       inhibitantion         is judged       inhibitantion         is judged       inhibitantion         SmPC for       inhibitantion         obsage       inhibitantion		may be				
Neratinib       inhibition by ritonavir.       Co-administra         Co-administra       iiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii						
Neratinib       ritonavir.         Co-administra       ion of         abemaciclib       and ritonavir         should be       avoided. If         this co-       administration         is judged       unavoidable,         refer to the       abemaciclib         SmPC for       dosage		to CYP3A4				
Neratinib       ritonavir.         Co-administra       ion of         abemaciclib       and ritonavir         should be       avoided. If         this co-       administration         is judged       unavoidable,         refer to the       abemaciclib         SmPC for       dosage		inhibition by				
Neratinib       tion of       abemaciclib         abemaciclib       and ritonavir         should be       avoided. If         this co-       this co-         administration       is judged         unavoidable,       refer to the         abemaciclib       abemaciclib         SmPC for       dosage						
Venetoclax       abemaciclib and ritonavir should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       abemaciclib abemaciclib SmPC for       abemaciclib abemaciclib should be abemaciclib smPC for       abemaciclib abemaciclib smPC for		Co-administra				
venetoclax       and ritonavir         venetoclax       administration         is judged       is judged         unavoidable,       is judged         refer to the       is judged         abemaciclib       is judged         SmPC for       is judged         dosage       is judged	Neratinib	tion of				
Venetoclax       should be avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       i		abemaciclib				
Venetoclax       avoided. If this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       is       is <td></td> <td>and ritonavir</td> <td></td> <td></td> <td></td> <td></td>		and ritonavir				
Venetoclax       this co- administration is judged unavoidable, refer to the abemaciclib SmPC for dosage       is       is </td <td></td> <td>should be</td> <td></td> <td></td> <td></td> <td></td>		should be				
Venetoclax       administration       is judged       is judged       is judged         unavoidable,       refer to the       is judged       is judged       is judged         abemaciclib       SmPC for       is judged       is judged       is judged         dosage       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged       is judged       is judged         is judged       is judged       is judged       is judged       is judged       is judged       is judged       is judged						
is judged unavoidable, refer to the abemaciclib SmPC for dosage						
unavoidable,       image	Venetoclax					
refer to the       abemaciclib         SmPC for       abemaciclib         dosage       abemaciclib						
abemaciclib     SmPC for       dosage     Image: Constraint of the second seco						
SmPC for     dosage						
dosage						

	Health Prod	ucts R	egulat	ory A	uthority		 	 
adjustment								
recommendat								
ions. Monitor								
for ADRs								
related to								
abemaciclib.								
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-administer								
ed with								
ritonavir								
resulting in								
the potential								
for serious								
adverse								
events								
including								
seizure.								
Concomitant								
use of								
ritonavir with								
apalutamide								
is not								
recommende								
d.								
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								

F		Health Prod	ucts R	egulatory	Authority			 
	Summary of							
	Product							
	Characteristics							
	for dosage							
	adjustment							
	recommendat							
	ions. Monitor							
	for ADRs							
	related to							
	ceritinib.							
	Serum							
	concentrations							
	may be							
	increased							
	when							
	co-administer							
	ed with							
	ritonavir							
	resulting in							
	the potential							
	for increased							
	incidence of							
	adverse							
	reactions.							
	reactions.							
	Serum							
	concentrations							
	may be							
	increased							
	when							
	co-administer							
	ed with							
	ritonavir							
	which may increase the							
	risk of toxicity,							
	including the risk of serious							
	adverse							
	events such							
	as QT interval							
	prolongation. Co-administra							
	tion 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							

		Health Prod	ucts Regula	tory A	Authority				 
	safety.								
	Co-administr	a							
	tion of								
	fostamatinib								
	with ritonavi								
	may increase								
	fostamatinib								
	metabolite								
	R406								
	exposure								
	resulting in								
	dose-related								
	adverse								
	events such								
	as								
	hepatotoxicit	Ŋ,							
	neutropenia								
	hypertension								
	or diarrhoea.								
	Refer to the								
	fostamatinib								
	SmPC for								
	dose								
	reduction								
	recommenda	.+							
	ions if such	11							
	events occur								
	Comuna								
	Serum								
	concentratio	ns							
	of ibrutinib								
	may be								
	increased du	e							
	to CYP3A								
	inhibition by								
	ritonavir,								
	resulting in								
	increased ris	<							
	for toxicity								
	including risk	C							
	of tumor lysi								
	syndrome.								
	Co-administr	a							
	tion of								
	ibrutinib and								
	ritonavir								
	should be								
	avoided. If th								
	benefit is								
	considered to			1					
	outweigh the	:							
	risk and	.		1					
	ritonavir mus	it							
	be used,								
	reduce the			1					
	ibrutinib dos	e							
	to 140 mg								
	and monitor			1					
	patient			1					
	closely for								
April 2024		CRN00F7Y1				Page 30	of 76		
-						-			

ŀ	Health Produ	ucts Reg	julatory A	Authority			
toxicity.							
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).							
Serum							
concentrations							
may be							
increased due							
to CYP3A							
inhibition by							
ritonavir,							
resulting in							
increased risk							
of tumor lysis							
syndrome at							
the dose							
initiation and							
during the							
ramp-up							
phase (see section 4.3							
and refer to							
the							
venetoclax							
SmPC).							
For patients							
who have							
completed							
the ramp-up							
phase and are							
on a steady							
daily dose							
of venetoclax,							
reduce the							
venetoclax							
dose by at							
least 75%							
when used							
with strong							

		Health Proc	ducts R	egula	tory A	uthority					<b>—</b> —1
	CYP3A inhibitors (refer to the venetoclax SmPC for dosing										
Anticoagula	instructions).										$\left  - \right $
Anticoagula nt											
				600							$\square$
Rivaroxaban	10, single dose			q1 2h		153%			155%		
Vorapaxar	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodyn amiceffects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban. Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministrati on of vorapaxar with Ritonavir is not recommended (see section 4.4 and refer to the vorapaxar Summary of Product Characteristic s).										
Warfarin S-Warfarin 04 April 2024	5, single dose	CRN00F7Y1		400		19%	Page 32	of 76	↓9%		
0 <del>4</del> Αμπ 2024							i aye 52	0170			

		Health Prod	ducts R		tory A I	luthority					
				q1							
D \\/				2h		1220/					$\left  - \right $
R-Warfarin	Induction of					↓33%			$\leftrightarrow$		$\vdash$
	CYP1A2 and										
	CYP2C9 lead										
	to decreased										
	levels of										
	Rwarfarin										
	while little										
	pharmacokine										
	tic effect is										
	noted on S-										
	warfarin when										
	co-administer										
	ed with										
	ritonavir.										
	Decreased										
	R-warfarin										
	levels may lead to										
	reduced										
	anticoagulatio										
	n, therefore it										
	is										
	recommended	1									
	that										
	anticoagulatio	n									
	parameters										
	are monitored										
	when warfarin										
	is										
	co-administer										
	ed with										
	ritonavir										
	dosed as an										
	antiretroviral										
	agent or as a										
	pharmacokine tic enhancer.										
Anticonvuls											┢┤
ants											
	Ritonavir										┢┤
	dosed as a										
	pharmacokine										
	tic enhancer										
	or as an										
	antiretroviral										
	agent inhibits										
	CYP3A4 and										
Carbamazepi	as a result is										
ne	expected to										
	increase the										
	plasma concentrations										
	of										
	carbamazepin										
	e. Careful										
	monitoring of										
	therapeutic										
04 April 2024	, <u>, , , , , , , , , , , , , , , , , , </u>	CRN00F7Y1		•	•		Page 33	of 76		•	·1
-							-				

		Health Proc	lucts R	egulat	ory A	uthority	 			
	and adverse									
	effects is									
	recommended									
	when									
	carbamazepine									
	is									
	concomitantly									
	administered									
	 with ritonavir.									-
	Ritonavir									
	dosed as a									
	pharmacokine									
	tic enhancer									
	or as an									
	antiretroviral									
	agent induces									
	oxidation by									
	CYP2C9 and									
	glucuronidati									
	on and as a									
	result is									
	expected to									
	decrease the									
Disalar	plasma									
Divalproex,	concentrations									
lamotrigine,	of									
phenytoin	anticonvulsan									
	ts. 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.									
Antidepress										$\vdash$
ants										
ants	Ritonavir									$\vdash$
	dosed as an									
	antiretroviral									
	agent is likely									
	to inhibit									
Amitriptyline,	CYP2D6 and									
fluoxetine,	as a result is									
imipramine,	expected to									
nortriptyline,	increase									
paroxetine,	concentrations									
sertraline	of									
	imipramine,									
	amitriptyline,									
	nortriptyline,									
	fluoxetine,									
	paroxetine or									
			1					1	1	1

		Health Produc	cts Regulat	tory Authority	/				
	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).								
			500						
	100, single			.1.150/			4220/		
Desipramine	oral dose		q1	145%			122%		
			2h						
+	The AUC and	<u> </u>		<u> </u>	+				$\vdash$
	Cmax of the								1
	2-hydroxy								
	metabolite								
	were								
	decreased 15								
	and 67%,								
	respectively.								
	Dosage								
	reduction of								
	desipramine								
	is								
	recommended								
	when								
	co-administer								
	ed with								
	ritonavir								
	dosed as an								1
									1
	antiretroviral								
<b>├</b> ─── <b>├</b>	agent.								-
			200						
Trazodone	50, single			12.4-f			134%		1
	dose		q1	old			10 70		
			2h						
	An increase in								
	the incidence								
	in								1
	trazodone-rel								1
	ated adverse								1
	reactions was								1
	noted when								1
	co-administer								1
	ed with								
	ritonavir								
	dosed as an								1
	antiretroviral								1
	agent or as a								1
									1
	pharmacokine								
	tic enhancer.								
	If trazodone is								
04 April 2024		CRN00F7Y1			Page 35	(70			

		Health Proc	lucts R	egulat	tory A	uthority				
	co-administer					Ī				
	ed 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										
	Concentrations									
	of colchicine									
	are expected to increase									
	when									
	coadministered									
	with ritonavir.									
	Life-threateni									
	ng and fatal									
	drug									
	interactions									
	have been									
	reported in									
	patients									
	treated with									
Colchicine	colchicine and									
	ritonavir									
	(CYP3A4 and									
	P-gp									
	inhibition) in									
	patients with									
	renal and/or									
	hepatic									
	impairment									
	(see sections									
	4.3 and 4.4).									
	Refer to the									
	colchicine									
	prescribing									
	 information.									
Antihistami										
nes										$\square$
	Ritonavir									
	co-administra									
	tion is likely									
	to result in									
	increased									
Astemizole,	plasma									
terfenadine	concentrations									
	of astemizole									
	and									
	terfenadine									
	and is									
							Dama 20	- 170		ட

			Health Proc	lucts R	egulat	ory A	uthority			 <b></b> ,
	th	erefore <b>con</b>								
	tra	aindicated								
	(56	ee section								
Fexofenadine	Ri m P- m fe do ar ag ph tic re in co o fe	3). tonavir may odify glycoprotein nediated xofenadine flux when osed as an ntriretroviral gent or as a narmacokine c enhancer sulting in creased oncentrations f xofenadine. creased								
	fe lev lev tir in de	xofenadine vels may ssen over ne as duction evelops.								
Loratadine	do ph tic or ar ag CV a t ex in pl cc o Ca m th ar ef re w lo cc ac	tonavir beed as a harmacokine c enhancer as an htiretroviral gent inhibits (P3A and as result is spected to crease the asma oncentrations f loratadine. areful onitoring of erapeutic ad adverse fects is commended when ratidine is oncomitantly dministered th ritonavir.								
Anti-infecti										
ves										$\square$
		tonavir		]		Ī				
		o-administra								
Fusidic Acid		on is likely								
		result in								
		creased								
								- 170		<u>ل</u> لل

		Health Proc	ducts R	egulat	ory A	uthority				 
	plasma									
	concentrations									
	of both									
	fusidic acid									
	and ritonavir									
	and is									
	therefore <b>con</b>									
	traindicated									
	(see section									
	4.3).							 		 $\dashv$
					500					
Rifabutin <sup>1</sup>	150 daily						14-fol		î2.5-	
					q1		d		fold	
					2h					
25-0-										
desacetyl							10 fa		<b>↑1C</b>	
rifabutin							138-fo		16-f	
metabolite							ld		old	
	Due to the									┓
	large increase									
	in rifabutin									
	AUC, the									
	concomitant									
	use of									
	rifabutin with									
	ritonavir									
	dosed as an									
	antiretroviral									
	agent is <b>contr</b>									
	aindicated									
	(see section									
	4.3). The									
	reduction of									
	the rifabutin									
	dose to 150									
	mg 3 times									
	per week may									
	be indicated									
	for select									
	protease									
	inhibitors									
	when									
	co-administer									
	ed with									
	ritonavir as a									
	pharmacokine									
	tic enhancer.									
	The Summary									
	of Product									
	Characteristics									
	of the									
	co-administer									
	ed protease									
	inhibitorshould									
	be consulted									
	for specific									
	recommendat									
	ions.									
	Consideration									
	should be									
			L							

		Health Proc	lucts R	egula	tory A	uthority				
Rifampicin	given to official guidance on the appropriate treatment of tuberculosis in HIV-infected patients. Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administer ed 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 highdose ritonavir	Health Proc		egulat	ory A	uthority				
					400					
Voriconazole	200 q12h				q1 2h		↓ 82%		↓ 66%	
	200 q12h				100 q1 2h		↓ 39%		↓24%	
	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole									

Atovaquone       Atovaquone         Atovaquone       A			Health Prod	ucis R	egula	Ory A	uthonty	 	 	 
Atovaquone       Rionavir gius and anticolasion isona as a noministra idendiation dosed as a plamacokine tic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.       Image:		is <b>contraindic</b>								
Alovaquone Alovaquone Bedaquiine Alovaquone No native Alovaquone Rinavi Rina		ated due to								
Alovaquone Alovaquone Bedaquiine Alovaquone No native Alovaquone Rinavi Rina		reduction in								
Atovaquone Atovaquone Atovaquone Bedaquiline No numersi No numersi No Numersi Nu		voriconazole								
433       Co-administration of transcription of voriconazole and ritonavir dosed as a pharmacokine tic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.       Image: Constraint of the patient										
4.3).       Co-administra         tion of       voriconazole         and ritonavir       dosed as a         pharmacokine       tie enhancer         should be       avoided,         avoided,       unless an         assessment of       the         the patient       justifies the         use of       voriconazole         voriconazole       assessment of         the patient       justifies the         use of       voriconazole         voriconazole       and its and its and assessment of         the patient       justifies the         use of       voriconazole         voriconazole       and its and and its and and as a result is         expected to       decrease the         plasma       concentrations of         of       atovaquone         Careful monitoring of serum levels       serum levels         serum levels       serum levels         ortherapeutic       effects is recomminately         recommentation       sudy is available with ritonavir, with ritonavir, with ritonavir, with ritonavir, with ritonavir, and set available with ritonavir, and set avai										
Co-administra       Image: Co-administra         tion of       voriconazole         and ritonavir       dosed as a pharmacokine         technancer       should be avoided.         unless an       assessment of         the patient       justifies the use of voriconazole.         voriconazole.       Image: Co-administra in the patient         unless an aassessment of       Image: Co-administra in the patient         justifies the use of voriconazole.       Image: Co-administra in the patient         Ritonavir       dosed as a pharmacokine       Image: Co-administra in the patient         glucuronidati       and as a result is expected to decrease the plasma concentrations of atovaquone.       Image: Co-contrations of serum levels         Bedaquiline       of atovaquone is concentrations interaction is tudy is available with ritonavir.       Image: Concentration is tudy is available with ritonavir.										
ion of voriconazole       and ritonavir       and ritonavir       and ritonavir         dosed as a       pharmacckine       and ritonavir         should be       avoided.       avoided.         avoided.       unless an       assessment of the       avoided.         unless an       assessment of the       assessment of the       avoided.         voriconazole       voriconazole.       avoided.       avoided.         voriconazole.       voriconazole.       avoided.       avoided.         voriconazole.       avoided.       avoided.       avoide.         voriconazole.       avoided.       avoide.       avoide.         voriconazole.       avoide.       avoide.       avoide.         voriconazole.       avoide.       avoide.       avoide.         voriconazole.       avoide.       avoide.       avoide.         voriconazole.       avoide.       avoide.       avoide. <t< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></t<>										
and ritonavir       dosed as a pharmacokine         dosed as a pharmacokine       tic enhancer         should be       avoided,         unless an       assessment of         the patient       benefit/risk to         the patient       benefit/risk to         use of       voriconazole.         voriconazole       voriconazole         Ritonavir       dosed as a pharmacokine         dosed as a pharmacokine       it is not parmacokine         dosed as is not parmacokine       it is not parmacokine										
and ritonavir dosed as a pharmacokine tic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.       Image: Construction of the patient pharmacokine tic enhancer or as an antiretroviral agent induces glucuronidati on and as a result is expected to decrease the plasma concentrations of atovaquone       Image: Construction of atovaquone       Image: Construction of atovaquone         Atovaquoe       Image: Construction of atovaquone       Image: Construction of atovaquone       Image: Construction of atovaquone       Image: Construction of atovaquone         Atovaquoe       Image: Construction of atovaquone is concomitantly administered with ritonavir, interaction study is available with ritonavir, interaction       Image: Construction of available with ritonavir, interaction study is available with       Image: Construction of available with ritonavir, interaction study is available with										
Atovaquone Atovaquone Careful Sedaquiline No										
Atovaquone Atovaquone Bedaquiline No										
Atoxaquone Atoxaquone Atoxaquone Careful Careful Careful Concomitation C										
Atovaquone       Careful concentrations of the pagent justifies the use of working of assessment of the benefit/fisk to the patient justifies the use of working of assessment of the patient patient is use of working of assessment of the patient is use of working of assessment of the patient is use of the pharma cokine the enhancer of as an antiretroviral agent induces glucuronidati on and as a result is expected to decrease the plasma concentrations of atovaquone.       No         Atovaquone       Careful monitoring of seconcentrations of atovaquone is concomitantly available with ritonavir,       No										
avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.       Image: Construction of the patient of the patient of the patient of the patient of the patient of the patient of the voriconazole.       Image: Construction of the patient of the pa										
Atovaquone Atovaquone Bedaquiline No										
Atovaquone Atovaquone Bedaquiline No Interaction Study is		avoided,								
Atovaquone       Atovaquone       Atovaquone       Atovaquone       Image: state st		unless an								
Atovaquone       Atovaquone       Careful       Image: State in the state in		assessment of								
Atovaquone       Atovaquone         Bedaquiline       No         No       interaction         No       interaction         Study is available with ritonavir.		the								
Atovaquone       Atovaquone         Bedaquiline       No         No       interaction         No       interaction         Study is available with ritonavir.		benefit/risk to								
Atovaquone       Careful monitoring of serum levels or therapeutic effects is recommended with ritonavir.       No         No       No       Interaction study is available with ritonavir.										
use of voriconazole.       woriconazole.       Image: state of the state										
Image: concentration of the second of the										
Atovaquone       Ritonavir dosed as a pharmacokine tic enhancer or as an antiretroviral agent induces glucuronidati on and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels o r therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.       Image: Ima										
Atovaquone Careful monitoring of serum levels of the repeatic effects is recommended when atovaquone is concentrations of the result is expected to decrease the plasma concentrations of serum levels of the result is recommended when atovaquone is concomitantly administered with ritonavir.		vonconazore.								_
Atovaquone Careful monitoring of serum levels of the repeatic effects is recommended when atovaquone is concentrations of the result is expected to decrease the plasma concentrations of serum levels of the result is recommended when atovaquone is concomitantly administered with ritonavir.		Pitopovir								
Atovaquone       Careful         Bedaquiline       or thrapeutic         or thrapeutic       of the commended         when       atovaquone is concomitantly         administered       administered         with ritonavir.       or the commended         with ritonavir. </th <th></th>										
tic enhancer       or as an         antiretroviral         agent induces         glucuronidati         on ad as a         result is         expected to         decrease the         plasma         concentrations         of         Atovaquone         Careful         monitoring of         serum levels         serum levels         of therapeutic         effects is         recommended         when         atovaquone is         concomitantly         adiministered         with ritonavir.										
Atovaquone       atovaquone.         Careful       monitoring of serum levels         Bedaquiline       or thrapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.         No       interaction study is available with ritonavir.										
Atovaquone Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone Atovaquone. Bedaquiline Or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.										
Atovaquone atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone atovaquone. Careful monitoring of serum levels Bedaquiline or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Atovaquone plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is conconitantly administered with ritonavir.										
Atovaquone       of       atovaquone.       atovaquone.         Careful       monitoring of       serum levels       atovaquone.         Bedaquiline       or therapeutic       effects is       recommended         when       atovaquone is       concomitantly       adovaquone is       atovaquone is         Concomitantly       administered       with ritonavir.       administered       administered         No       interaction       study is       available with ritonavir only.       available with ritonavir only.       administered		decrease the								
Atovaquone       of       atovaquone.       atovaquone.       atovaquone.         Careful       monitoring of       serum levels       or therapeutic       effects is         or therapeutic       effects is       recommended       when       atovaquone is         atovaquone is       concomitantly       administered       with ritonavir.       interaction         No       interaction       study is       available with       interaction       interaction		plasma								
Atovaquone Bedaquiline Bedaquiline Bedaquiline Bedaquiline Bodaquiline Bedaquiline Bedaquiline Bodaquiline Bedaquiline Bodaqui		concentrations								
Bedaquiline		of								
Bedaquiline	Atovaquone	atovaquone.								
Bedaquiline monitoring of serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.										
Bedaquiline serum levels or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.		monitoring of								
Bedaquiline       or therapeutic effects is recommended when atovaquone is concomitantly administered with ritonavir.       Image: Concomitant of the second										
effects is recommended when atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.	Bedaguiline									
recommended when atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.										
when atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.										
atovaquone is concomitantly administered with ritonavir. No interaction study is available with ritonavir only.										
concomitantly administered with ritonavir. No interaction study is available with ritonavir only.										
administered with ritonavir. No interaction study is available with ritonavir only.										
with ritonavir.       No         interaction       study is         available with       ritonavir only.										
No interaction study is available with ritonavir only.										
interaction study is available with ritonavir only.		with ritonavir.								
interaction study is available with ritonavir only.										
interaction study is available with ritonavir only.										
study is       available with       ritonavir only.										
available with ritonavir only.										
ritonavir only.										
In an In										
		In an								

		Health Proc	iucis R	egula	OTY P	uthonty		 i		 
	interaction									
	study of									
	single-dose									
	bedaquiline									
	and multiple									
	dose									
	lopinavir/riton									
	avir, 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-administra									
	tion. Due to									
	the risk of									
	bedaquiline									
	related									
	adverse									
	events,									
	co-administra									
	tion should									
	be avoided. If									
	the benefit									
	outweighs the									
	risk,									
	co-administra									
	tion of									
	bedaquiline									
	with ritonavir									
	must be done									
	with caution.									
	More									
	frequent									
	electrocardio									
	gram									
	monitoring									
	and									
	monitoring of									
	transaminases									
	is									
	recommended									
	(see section									
	4.4 and									
	referto the									
	bedaquiline									
	Summary of									
	Product									
	Characteristic									
	s).									
	-,.									
Clarithromusi	E00 ~12h				200		↑770/		131%	
Clarithromyci	500 q12h				200		177%		131%	

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i		Health Prod	ucts Re	egulatory	<u>/ Αι</u>	uthority				
n				3p	3					
				h						
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-administer									
	ed with									
	ritonavir									
	dosed as an									
	antiretroviral									
	agent or as a									
	pharmacokine									
	tic 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%.									
					Γ					
Delamanid	No									
	interaction									
	study is									
04 Ameril 2024							Dere 12	-170		

	Health Products Regulatory Authority	_
	available with	
	ritonavir only.	
	In a healthy	
	volunteer	
	drug	
	interaction	
	study of	
	delamanid	
	100 mg twice	
	daily and	
	lopinavir/riton	
	avir 400/100	
	mg twice	
	daily for 14	
	days, the	
	exposure of	
	the line line line line line line line lin	
	delamanid	
	metabolite	
	DM-6705 was	
	30%	
	increased.	
	Due to the	
	risk of QTc	
	prolongation	
	associated	
	with	
	DM-6705, if	
	co-administra	
	tion of	
	delamanid	
Fruthramusin	with ritonavir	
Erythromycin, itraconazole	is considered necessary,	
	very frequent	
	ECG	
	monitoring	
	throughout	
	the full	
	delamanid	
	treatment	
	period is	
	recommended	
	(see section	
	4.4 and refer	
	to the	
	delamanid	
	Summary of	
	Product	
	Characteristic	
	s).	
	Ritonavir	
	dosed as a	
	pharmacokine	
	tic enhancer	
	or as an	
	antiretroviral	
	agent inhibits	
	CYP3A4 and	

	•	Health Proc	lucts F	legula	tory A	uthority				
	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.									
					50					
Ketoconazol	200 daily				0q		13.4-f		155%	
e					12		old		15570	
					h					 Ш
	Ritonavir									
	inhibits									
	CYP3A-media									
	ted									
	metabolism									
	of									
	ketoconazole.									
	Due to an									
	increased									
	incidence of									
	gastrointestin									
	al and hepatic									
	adverse									
	reactions, a									
	dose									
	reduction of									
	ketoconazole									
	should be									
	considered									
	when									
	co-administer									
	ed with									
	ritonavir									
	dosed as an									
	antiretroviral									
	agent or as a									
	pharmacokine									
	tic enhancer.									
Sulfamethox		1			50					$\square$
azole/	800/160,				0q		↓20%			
Trimethopri	single dose				12		/		$\leftrightarrow$	
m <sup>2</sup>					h		120%			
1 (1)										

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		Health Prod	ucts R	egulat	ory A	uthority		 	 	
	Dose									
	alteration of									
	sulfamethoxa									
	zole/trimetho									
	prim during									
	concomitant									
	ritonavir									
	therapy									
	should not be									
	necessary.									
Antipsychot										
ics/Neurole										
ptics										
	Ritonavir									
	co-administra									
	tion is likely									
	to result in									
	increased									
	plasma									
Clozapine,	concentrations									
pimozide	of clozapine									
	or pimozide									
	and is									
	therefore <b>con</b>									
	traindicated									
	(see section									
	4.3).								 	
	Ritonavir									
	dosed as an									
	antiretroviral									
	agent is likely									
	to inhibit									
	CYP2D6 and									
	as a result is									
	expected to									
	increase									
	concentrations									
	of									
	haloperidol,									
	risperidone									
Haloperidol,	and									
risperidone,	thioridazine.									
thioridazine	Careful									
	monitoring of									
	therapeutic									
	and adverse									
	effects is									
	recommended									
	when these									
	medicines are									
	concomitantly									
	administered									
	with									
	antiretroviral									
	doses of									
	ritonavir.									
	Due to CYP3A									
	inhibition by									
Lurasidone	ritonavir,									
04 April 2024	concentrations	RN00F7Y1					Page 45			

		Health Prod	lucts R	egula	tory A	uthority	 		 
	of lurasidone								
	are expected								
	to increase.								
	The								
	concomitant								
	administration								
	with								
	lurasidone is								
	contraindicate	a							
	(see section								
	4.3).								
	Due to CYP3A								
	inhibition by								
	ritonavir,								
	concentrations	5							
	of quetiapine								
	are expected								
	to increase.								
	Concomitant								
	administration								
Quetiapine	of ritonavir								
2	and								
	quetiapine is								
	contraindicate	d							
	as it may	G							
	increase								
	quetiapine-rel								
	ated toxicity								
	(see section								
	4.3).								
ß2-agonist									
(long									
acting)									
	Ritonavir								
	inhibits								
	CYP3A4 and								
	as a result a								
	pronounced								
	increase in								
	the plasma								
Salmeterol	concentrations	5							
	of salmeterol								
	is expected.								
	Therefore								
	concomitant								
	use is not								
	recommende								
	d.								
Calcium						L			
channel									
antagonists									$\vdash$
	Ritonavir								
	dosed as a								
Amlodipine,	pharmacokine								
diltiazem,	tic enhancer								
nifedipine	or as an								
meaipine	antiretroviral								
	agent inhibits								
	CYP3A4 and								

·			Health Proc	lucts R	egula	tory A	uthority	1	1	1		
		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.										
		with fitofiavit.										
Endothelin												
antagonists												 $\vdash$
		Co-administra										
		tion of										
		bosentan and										
		ritonavir may										
		increase										
		steady state										
		bosentan										
		maximum										
		concentrations										
		(Cmax) and										
		area under										
		the curve										
		(AUC).										
		Serum										
		concentrations										
Bosentan		may be										
DOSEIIIan		increased due										
Dissionst												
Riociguat		to CYP3A and										
		P-gp										
		inhibition by										
		ritonavir. The										
		coadministrati										
		on of										
		riociguat with										
		Ritonavir is										
		not										
		recommended										
		(see section										
		4.4 and refer										
		to riociguat										
		Summary of										
		Product										
		Characteristic										
		s).										
Ergot												$\vdash$
Derivatives												
Dihydroergo		Ritonavir										 ┢╌╢
tamine,		co-administra										
04 April 2024	ļ		CRN00F7Y1	I	I	l		Page 47	of 76	ļ	I	ш
04 April 2024								i aye 47	0170			

· · · · · · · · · · · · · · · · · · ·	Health Products Re	gulatory Author	ity	 
tion is likely				
to result in				
increased				
plasma				
ergonovine, concentrat	ons			
ergotamine, of ergot				
methylergon derivatives				
ovine and is				
therefore <b>c</b>	on			
traindicate				
(see section				
4.3).				
GI motility				1
agent				
	Ritonavir			
	co-admini			
	stration is			
	likely to result in			
	increased			
	plasma			
Circurvida	concentra			
Cisapride	tions of			
	cisapride			
	and is			
	therefore			
	contraind			
	icated			
	(see			
	section			
	4.3).			
HCV Direct				
Acting				
Antiviral				
	Serum			
	concentra			
	tions may			
	be			
	increased			
	due to			
	P-glycopr			
	otein,			
	BCRP and			
	OATP1B			
	inhibition			
	by			
Glecaprevir/	ritonavir.			
pibrentasvir	Concomit			
	ant			
	administr			
	ation of			
	glecaprevi			
	r/pibrenta			
	svir and			
	Ritonavir			
	tablets is			
	not			
	recomme			
				1 1
	nded due to an			

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	Health Products	s Regula	tory A	uthority				
	increased							
	risk of ALT							
	elevations							
	associated							
	with							
	increased							
	glecaprevir							
	exposure.							
нси								
Protease								
Inhibitor								
			10					
			0q		17.2-f		<u></u> 14.7-	
Simeprevir	200 qd		12		old		fold	
			h				1010	
	Ritonavir							
	increases							
	plasma							
	concentra							
	tions of							
	simeprevir							
	as a result							
	of							
	CYP3A4							
	inhibition.							
	lt is not							
	recomme							
	nded to							
	co-admini							
	ster							
	ritonavir							
	with							
	simeprevi							
	r.							
HMG Co-A								
Reductase								
Inhibitors								
	HMG-CoA							
	reductase							
	inhibitors							
	which are							
	highly							
	dependent							
	on CYP3A							
	metabolis							
Atorvastatin,	m, such as							
Fluvastatin,	lovastatin							
	and							
Lovastatin,								
Pravastatin,	simvastati							
Rosuvastatin,	n, are							
Simvastatin	expected							
	to have							
	markedly							
	increased							
	plasma							
	concentra							
	tions							
	when							
	co-admini							1

		Health Prod	ucts Re	gulator	Authori	ty		 	
		stered							
		with							
		ritonavir							
		dosed as							
		an							
		antiretrovi							
		ral agent							
		or as a							
		pharmaco							
		kinetic							
		enhancer.							
		Since							
		increased							
		concentra							
		tions of							
		lovastatin							
		and							
		simvastatin							
		may							
		predispose							
		patients							
		to							
		myopathi							
		es,							
		including							
		rhabdomy							
		olysis, the							
		combinati							
		on of							
		these							
		medicinal							
		products							
		with							
		ritonavir is							
		contraind							
		icated							
		(see							
		section							
		4.3).							
		Atorvastat							
		in is less							
		dependent							
		on CYP3A							
		for							
		metabolis							
		m. While							
		rosuvastat							
		in							
		elimination							
		is not							
		dependent							
		on							
		CYP3A, an							
		elevation							
		of							
		rosuvastat							
		in							
		exposure							
		has been							
		reported							

		Health Proc	lucts R	egulat	ory A	uthority			
		with							
		ritonavir							
		coadminis							
		tration.							
		The							
		mechanism							
		of this							
		interaction							
		is not							
		clear, but							
		may be							
		the result							
		of							
		transporter							
		inhibition.							
		When							
		used with							
		ritonavir							
		dosed as							
		а							
		pharmaco							
		kinetic							
		enhancer							
		or as an							
		antiretrovi							
		ral agent,							
		the lowest							
		possible							
		possible							
		doses of							
		atorvastatin							
		or							
		rosuvastat							
		in should							
		be							
		administe							
		red. The							
		metabolism							
		of							
		pravastatin							
		and							
		fluvastatin							
		is not							
		dependent							
		on							
		CYP3A,							
		and							
		interactio							
		ns are not							
		expected							
		with							
		ritonavir.							
		lf							
		treatment							
		with an							
		HMG-CoA							
		reductase							
		inhibitor							
		is							
		indicated,							
		pravastatin							
 <u> </u>	I								

	Health Product	ts Regula	tory A	uthority				
	or							
	fluvastatin							
	is							
	recomme							
	nded.							
Hormonal								
contracepti								
ve			500					
	50 µg,		500					
Ethinyl	single				↓ 40%		↓ 32%	
estradiol	dose		q1					
		_	2h					
	Due to							
	reductions							
	in ethinyl							
	estradiol							
	concentra							
	tions,							
	barrier or							
	other							
	non-horm							
	onal							
	methods							
	of							
	contracep							
	tion							
	should be							
	considered							
	with							
	concomita							
	nt							
	ritonavir							
	use when							
	dosed as							
	an							
	antiretrovi							
	ral agent							
	or as a							
	pharmaco							
	kinetic							
	enhancer.							
	Ritonavir							
	is likely to							
	change							
	the							
	uterine							
	bleeding							
	profile							
	and							
	reduce							
	the							
	effectiven							
	ess of							
	estradiol-							
	containing							
	contractor							
	contracep							
	tives (see							
	section							
	4.4).				Dere 52			

	i	Health Products Regulatory Authority	— <u> </u>
Immunosup			
pressants			
		Ritonavir	
		dosed as	
		a l l l l l l l l l	
		pharmaco	
		kinetic	
		enhancer	
		or as an	
		antiretrovi	
		ral agent	
		inhibits	
		CYP3A4	
		and as a	
		result is	
		expected	
		to	
		increase	
		the	
		plasma	
		concentra	
		tions of	
Cuclosporing			
Cyclosporine,		cyclospori	
tacrolimus,		ne,	
everolimus		tacrolimus	
		or	
		everolimu	
		s. Careful	
		monitoring	
		of	
		therapeutic discussion of the second s	
		and	
		adverse	
		effects is	
		recomme	
		nded	
		when	
		these	
		medicines	
		are	
		concomita	
		ntly	
		administe	
		red with	
		ritonavir.	
Lipid-modif			-+
ying agents			
,		CYP3A4	
		inhibitors	
		increase de la companya de la	
		the he h	
		exposure	
		of land land land land land land land land	
Lomitapide		lomitapid	
·		e, with	
		strong	
		inhibitors	
		increasing	
		exposure	
		approxim	

	Health Products Regula	tory Authority				 -
	ately					
	27-fold.					
	Due to					
	СҮРЗА					
	inhibition					
	by					
	ritonavir,					
	concentra					
	tions of					
	lomitapide					
	are					
	expected					
	to					
	increase.					
	Concomit					
	ant use of					
	Ritonavir					
	tablets with					
	lomitapide					
	is					
	contraindi					
	cated (see					
	prescribing					
	information					
	for					
	lomitapid					
	e) (see					
	section					
	4.3).					
Phosphodie	4.5).					 ┥
sterase (PDE5)						
(PDE5) inhibitors						
Inhibitors		600				 +
		600	1		1 1	
Avanafil	50, single	~1	13-fol		2.4-f	
	dose	q1	d		old	
	Concomit	2h				 ┥
	ant use of					
	avanafil					
	with					
	ritonavir is					
	contraindi					
	cated (see					
	section					
	4.3).					 ┥
	100,	500	<b>↑</b>			
Sildenafil	single		11-fol		14-fo	
	dose	q1	d		ld	
		2h				 4
	Concomit					
	ant use of					
		1 1				
	sildenafil		1 1			
	for the					
	for the treatment					
	for the					

	1	Health Proc	lucts R	egulat	ory A	uthority				
		with								
		ritonavir								
		dosed as								
		an								
		antiretrovi								
		ral agent								
		or as a								
		pharmaco								
		kinetic								
		enhancer								
		should be								
		done with								
		caution								
		and in no								
		instance								
		should								
		sildenafil								
		doses								
		exceed 25								
		mg in 48								
		hours (see								
		also								
		section								
		4.4).								
		Concomit								
		ant use of								
		sildenafil								
		with								
		ritonavir is								
		contraind								
		icated in								
		pulmonary								
		arterial								
		hypertensi								
		on								
		patients								
		(see								
		section								
		 4.3).			200					$\vdash$
					200					
Tadalafil		20, single					124%		$\leftrightarrow$	
		dose			q1		-			
		-			2h					
		The								
		concomita								
		nt use of								
		tadalafil								
		for the								
		treatment								
		of erectile								
		dysfunction								
		with								
		ritonavir								
		dosed as								
		an								
		antiretrovi								
		ral agent								
		or as a								
		pharmaco								
		kinetic								
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enhancer       enhancer       enhancer         with       caution at reduced       reduced         doses of no more than 10       more than 10       enhancer         burs       with         increased monitoring for adverse reactions (see section 14).       enhancer         section       4.4).         When tadalafil is used       enhancer         usid       used         section       4.4).         When tadalafil is used       enhancer         usid       used         sites       section         vardenafil       enhancer         burst       enhancer         vardenafil       enhancer         vardenafil       for column with mitnarteria         vardenafil       enhancer         vardenafil       for column with mitnarteria         vardenafil       enhancer         vardenafil       enhancer         vardenafil       enhancer         sites       enhancer         vardenafil       enhancer         use of vardenafil       enhancer         use of vardenafil       enhancer         use of vardenafil       enhancer         uset of       enhancer			 Health Prod	lucts R	egulat	ory A	uthority				
Vardenafil       Single       600       149-fo       113-f         Vardenafil       Concomit       Amage       Amage       Amage       Amage         Vardenafil       Concomit       Single       G1       149-fo       113-f       old         Vardenafil       Single       Gase       G1       149-fo       113-f       old       113-f         Vardenafil       Concomit       Amage       Amage       Amage       Amage       Amage       Amage       Amage         Vardenafil       Concomit       Single       G1       149-fo       113-f       old       113-f       old       Image			enhancer								
Vardenafil       Single       600       149-fo       113-f         Vardenafil       Concomit       Amage       Amage       Amage       Amage         Vardenafil       Concomit       Single       G1       149-fo       113-f       old         Vardenafil       Single       Gase       G1       149-fo       113-f       old       113-f         Vardenafil       Concomit       Amage       Amage       Amage       Amage       Amage       Amage       Amage         Vardenafil       Concomit       Single       G1       149-fo       113-f       old       113-f       old       Image			should be								
vardenafil       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 concurren tly with ritonavir in patients with pulmonary arterial hypertensi on, refer to the tadalafil Summary of Product Characteri stics.       600 149-fo 2h       149-fo do       113-f old											
Vardenafil       Image: concurrent transmission on concertation on more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions (see section 4.4).       Image: concurrent transmission on refere to the tadalafil is used concurrent transmission, refere to the tadalafil Summary arterial hypertensi on, refere to the tadalafil Summary arterial his concurrent stics.       Image: concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission, refere to the tadalafil Summary arterial his concurrent transmission, refere to the tadalafil Summary arterial his concurrent transmission, refere to the tadalafil Summary of Product Characteri stics.       Image: concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission, refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary of Product Characteri stics.       Image: concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmission on refere to the tadalafil Summary arterial his concurrent transmissi concurrent transmission on refere to the tadalafil Sum											
Vardenafil       Image: section in the section is the section in the section is the se											
Vardenafil       S. Single       600       149-fo       113-f         Vardenafil       S. Single       800       149-fo       113-f       113-f         Vardenafil       S. Single       800       149-fo       113-f       113-f											
Vardenafil       S       S       S       600       149-fo       113-f         Vardenafil       Concomit       ant use of       accomit       ant use of       accomit       accomit         Vardenafil       Concomit       ant use of       accomit       acco			doses of								
Vardenafil       S. single       S. single       600       149-fo       103-f       113-f         Vardenafil       S. single       S. single       600       149-fo       103-f       113-f         Vardenafil       S. single       S. singl			no more								
Vardenafil       S. single       S. single       600       149-fo       103-f       113-f         Vardenafil       S. single       S. single       600       149-fo       103-f       113-f         Vardenafil       S. single       S. singl			than 10								
Vardenafil       S, single       600       149-fo       113-f         Sites of vardenafil       Vardenafil       S, single       600       149-fo       113-f         Vardenafil       S, single       600       149-fo       113-f       old       113-f         Vardenafil       S, single       600       149-fo       113-f       0d       113-f         Sites       Sites       Sites       Sites       Sites       Sites       Sites       Sites       Sites         Sites </td <td></td>											
very 72       hours       with         increased       monitoring         for       adverse         reactions       (see         section       4.4).         When       tadalafil is         used       concurren         tty with       ritonavir         in patients       with         with       pulmonary         arterial       hypertensi         on, refer       on, refer         to the       tadalafil         Summary       of Product         Characteri       stics.         Vardenafil       Single         dose       a1         with       in use of         vardenafil       Concomit         ant use of       vardenafil         with       in use of         vardenafil       istaded         istaded       ist											
hours       hours         with       increased         monitoring       for         adverse       reactions         (see       section         section       4.4).         When       tadalfil is         used       concurren         thy with       ritonavir         in patients       with         pulmonary       arterial         hypertension       on, refer         to the       tadalfil         Summary       of Product         Characteri       g1         stics.       g1         Vardenafil       concomit         ant use of       yardenafil         with       ritonavir is         contraind       in use of         vardenafil       in use of         in tuse of       in use of         vardenafil       in use of         in tuse of       in use of         vardenafil       in use of         in tuse of       in use of         in tuse of       in use of         in tadalfil       in use of         in tuse of       in use of         in tuse of       in use of <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>											
Vardenafil       S, single       600       149-fo       113-f         Vardenafil       S, single       1											
Vardenafil       Concomit       Single       600       149-fo       113-f         Vardenafil       Concomit       31       21       21       149-fo       113-f         Vardenafil       Concomit       31       21											
Vardenafil       S. single       600       149-fo       113-f         Vardenafil       S. single       1       1       1       1       1         Vardenafil       S. single       1			with								
Vardenafil       Concomit and use of vardenafil is used       600       149-fo       113-f       old       113-f			increased								
Vardenafil       Concomit and use of vardenafil is used       600       149-fo       113-f       old       113-f			monitorina								
Vardenafil       Image: section sectio											
Vardenafil       S. single       600       149-fo       113-f       113-f       old       113-f       o											
Vardenafil       Single       600       149-fo       113-f         Vardenafil       Concomit       600       149-fo       113-f         Vardenafil       Concomit       1       113-f       old         Vardenafil       Concomit       1       113-f       old       113-f         Vardenafil       Concomit       1       1       1       1       1         Vardenafil       Concomit       1       1       1       1       1       1         Image: Single       Single       Single       1											
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4.4).       When       tadalafil is       used       is											
Vardenafil       S, single       S, single       600       149-fo       113-f       113-f <td></td> <td></td> <td>section</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>			section								
Vardenafil       S, single       S, single       600       149-fo       113-f       113-f <td></td> <td></td> <td>4.4).</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>			4.4).								
VardenafilS. single dose600 a1 a1 concurrin diama succession149-fo old113-f oldVardenafilS. single doseAA <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>											
VardenafilUsed concurren tly with in patients with pulmonary arterial hypertensi on, refer to the tadalafilImage: Concurrent ty with pulmonary arterial hypertensi on, refer to the tadalafilImage: Concurrent ty with pulmonary arterial hypertensi on, refer to the tadalafilImage: Concurrent ty with pulmonary arterial hypertensi on, refer to the tadalafilImage: Concurrent ty with pulmonary arterial by pulmonary arterial hypertensi on, refer to the tadalafil doseImage: Concurrent ty with the the pulmonary arterial by pulmonary 											
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VardenafilConcomit and use of vardenafilABB <td></td>											
Vardenafil       Concomit ant use of vardenafil       A       <											
VardenafilConcomit ant use of vardenafil600 and use of vardenafil149-fo old113-f <b< td=""><td></td><td></td><td>tly with</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></b<>			tly with								
VardenafilConcomit ant use of vardenafil600 and use of vardenafil149-fo old113-f <b< td=""><td></td><td></td><td>ritonavir</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></b<>			ritonavir								
Vardenafil       Concomit ant use of vardenafil with ritonavir is contraind licated       Image: second sec											
VardenafilMarketM											
Vardenafil       A											
VardenafilMypertensi on, refer to the tadalafil Summary of Product Characteri stics.Image: Characteri of the tadalafil Summary of Product Characteri stics.Image: Characteri of the tadalafil Summary of Product Characteri stics.Image: Characteri of the tadalafil Summary of Product tadalafil Summary of Product Characteri stics.Image: Characteri tadalafil Summary of Product tadalafil Summary of Product Characteri stics.Image: Characteri tadalafil tadalafil stics.Image: Characteri tadalafil tadalafil tadalafil tadalafil tadalafil stics.Image: Characteri tadalafil <											
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Vardenafilto the tadalafil Summary of Product Characteri stics.Image: Characteri stics.Image: Characteri stics.Image			hypertensi								
Vardenafilto the tadalafil Summary of Product Characteri stics.Image: Characteri stics.Image: Characteri stics.Image											
VardenafilLadalafilSummary of Product Characteri stics.SouthSout											
VardenafilSummary of Product Characteri stics.Summary of Product Characteri stics.Summary of Product Characteri stics.Summary of Product of Product <br< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></br<>											
Vardenafilof Product Characteri stics.of Product Stics.of Product S											
Vardenafil       Characteri stics.       Image: stics.											
Vardenafil       stics.       Image: Concomit ant use of vardenafil with ritonavir is contraind icated       Source of the contraind icate       S											
Vardenafil       5, single dose       600       149-fo       113-f       113-f       old       113-f       old       113-f       old       1			Characteri								
Vardenafil       5, single dose       600       149-fo       113-f       113-f       old       113-f       old       113-f       old       1			stics.								
Vardenafil       5, single dose       1       149-fo Id       113-f oId       113-f oId         Vardenafil       Concomit ant use of vardenafil with ritonavir is contraind icated       Image: Contraind icated </td <td></td> <td></td> <td></td> <td></td> <td></td> <td>600</td> <td></td> <td></td> <td></td> <td></td> <td></td>						600					
Vardenafil     dose     q1 2h     Id     old     old       Concomit ant use of vardenafil     Image: Concomit ant use			5 cinala			000		110 fo		10 f	
dose     q1     Id     old       2h     2h     Id     old	Vardenafil					~1					
Concomit ant use of vardenafil with ritonavir is contraind icated			aose			qı		Ia		010	
ant use of   vardenafil   with   ritonavir is   contraind   icated				$\mid$		2h					
vardenafil with ritonavir is contraind icated			Concomit								
vardenafil with ritonavir is contraind icated											
with ritonavir is contraind icated											
ritonavir is contraind icated											
contraind icated											
icated											
			icated								
(see			(see								
section											
4.3).											
	Sodatives /h			┝──┤							<u> </u>
Sedatives/h											
	ypnotics			$\mid$					ļ	 ļ	
Clorazepate, Ritonavir	Clorazepate.										
			co-admini								
		1									
	diazepam,		JUGUOITA								1
oral and result in	diazepam, estazolam,										1
Oral and         result in         Page 56 of 76           04 April 2024         CRN00F7Y1         Page 56 of 76	diazepam, estazolam, flurazepam,		likely to								

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CRN00F7Y1

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	-	•	Health Prod	ucts R	<u>egulat</u>	ory A	uthority			 
			increased							
			plasma							
			concentra							
			tions of							
			clorazepat							
			e,							
			diazepam,							
			estazolam							
			and							
			flurazepam							
			and is							
			therefore							
			contraind							
			icated							
			(see							
			section							
			4.3).							
			Midazolam							
			is							
			extensively							
			extensively							
			metabolis							
			ed by							
			CYP3A4.							
			Coadmini							
			stration							
			with							
			ritonavir							
			may cause							
parenteral			a large							
midazolam			increase							
			in the							
			concentra							
			tion of							
			this							
			benzodiaz							
			epine. No							
			medicinal							
			product							
			interaction							
			study has							
			been							
			performed							
			for the							
			co-admini							
			stration of							
			ritonavir							
			with							
			with benzodiaz							
			benzodiaz							
			benzodiaz epines.							
			benzodiaz epines. Based on							
			benzodiaz epines. Based on data for							
			benzodiaz epines. Based on data for other							
			benzodiaz epines. Based on data for other CYP3A4							
			benzodiaz epines. Based on data for other CYP3A4 inhibitors,							
			benzodiaz epines. Based on data for other CYP3A4							
			benzodiaz epines. Based on data for other CYP3A4 inhibitors, plasma concentra							
			benzodiaz epines. Based on data for other CYP3A4 inhibitors, plasma							
			benzodiaz epines. Based on data for other CYP3A4 inhibitors, plasma concentra tions of							
			benzodiaz epines. Based on data for other CYP3A4 inhibitors, plasma concentra							

		Health Proc	ucts R	egulat	ory A	uthority			 
		expected							
		to be							
		significant							
		ly higher							
		when							
		midazolam							
		is given							
		orally.							
		Therefore,							
		ritonavir							
		should							
		not be							
		co-admini							
		stered							
		with orally							
		administe							
		red							
		midazolam							
		(see							
		section							
		4.3),							
		whereas							
		caution							
		should be							
		used with							
		co-admini							
		stration of							
		ritonavir							
		and							
		parenteral							
		midazola							
		m. Data							
		from							
		concomita							
		nt use of							
		parenteral							
		midazolam							
		with							
		other							
		protease							
		inhibitors							
		suggest a							
		possible 3							
		- 4 fold							
		increase							
		in							
		midazolam							
		plasma							
		levels. If							
		ritonavir is							
		co-admini							
		stered							
		with							
		parenteral							
		midazola							
		m, it							
		should be							
		done in							
		an							
		intensive							
		IIICEIISIVE						 	

	Health Products Reg	ulatory Autho	ority			
	care unit					
	(ICU) or					
	similar					
	setting					
	which					
	ensures					
	close					
	clinical					
	monitoring					
	and					
	appropria					
	te medical					
	managem					
	ent in					
	case of					
	respiratory					
	depression					
	and/or					
	prolonged					
	sedation.					
	Dosage					
	adjustment					
	for					
	midazolam					
	should					
	be					
	considere					
	d,					
	especially					
	if more					
	than a					
	single					
	dose of					
	midazolam					
	is					
	administe					
	red.					
		20				
	0.125					
Triazalam	0.125,	0,	1>20		1070/	
Triazolam	single	4	fold		187%	
	dose	do				
<u>├</u> ───┤		ses				
	Ritonavir					
	co-admini					
	stration is					
	likely to					
	result in			1		I
	result in increased					
	increased					
	increased plasma					
	increased plasma concentra					
	increased plasma concentra tions of					
	increased plasma concentra tions of triazolam					
	increased plasma concentra tions of triazolam and is					
	increased plasma concentra tions of triazolam and is therefore					
	increased plasma concentra tions of triazolam and is					
	increased plasma concentra tions of triazolam and is therefore					
	increased plasma concentra tions of triazolam and is therefore <b>contraind</b> <b>icated</b>					
	increased plasma concentra tions of triazolam and is therefore <b>contraind</b> <b>icated</b> (see					
	increased plasma concentra tions of triazolam and is therefore <b>contraind</b> <b>icated</b>					

	Health Products Re		ity	
		500		
	50, oral			
Pethidine	single		↓62%	↓59%
	dose	q1		
ļ ļ	<u> </u>	2h		
Norpethidine			A 70/	*070/
metabolite			14 <b>7</b> %	187%
	The use of			
	pethidine			
	and			
	ritonavir is			
	contraind			
	icated			
	due to the			
	increased			
	concentra			
	tions of			
	the			
	metabolit			
	e,			
	norpethidi			
	ne, which			
	has both			
	analgesic			
	and CNS			
	stimulant			
	activity.			
	Elevated			
	norpethidi			
	ne			
	concentra			
	tions may			
	increase			
	the risk of			
	CNS			
	effects			
	(eg,			
	(eg, · 、			
	seizures),			
	see			
	section			
	4.3.	<u> </u>		
		200		
		q1		
Alprazolam	1, single	4'     26	12.5	
Alprazolam	dose	2h,	fold	$\leftrightarrow$
		2		
		da		
<u>├                                    </u>	++	ys	<del></del>	
		500		
		q1		
		<sup>4</sup>     <sub>2</sub>	1100/	↓16%
		2h,	↓12%	↓10%
		10		
		da		
		ys		+ + +
	Alprazolam			
	metabolism			
	was			
	inhibited			

following	
Ionowing	
the line line line line line line line lin	
introducti	
on 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 is in the second sec	
co-admini	
stered	
with	
ritonavir	
dosed as	
an a	
antiretrovi	
ral agent	
or as a	
pharmaco	
kinetic	
enhancer,	
before	
induction	
of	
alprazolam	
aiprazoiani	
metabolism	
Ditenzuir	
Ritonavir desed as	
dosed as	
a hormoso	
pharmaco	
kinetic	
enhancer	
or as an	
antiretrovi	
Buspirone ral agent	
CYP3A	
and as a	
result is	
expected	
to to to to to the second seco	
increase	
the	
plasma	

		Health Prod	lucts R	egulat	ory A	uthority				
		concentra								
		tions of								
		buspirone.								
		Careful								
		monitoring								
		of								
		therapeutic								
		and								
		adverse								
		effects is								
		recomme								
		nded								
		when								
		buspirone								
		concomita								
		ntly								
		administe								
		red with								
		ritonavir.								$\square$
Sleeping										
agent										Ш
					20					 
					0,					
Zolpidem		5			4		128%		122%	
Zoipidem		5			do		120/0		12270	
		7 1 1			ses					
		Zolpidem								
		and								
		ritonavir								
		may be								
		co-admini								
		stered								
		with								
		careful								
		monitoring								
		for								
		excessive								
		sedative								
		effects.								
Smoke										
cessation										
					100					
					.00					
Bupropion		150			<b>c</b> 1		↓22%		↓21%	
					q1 2h					
					2h					⊢
					600					
		150					166%		↓62%	
		150			q1		↓UU /0		+0∠/0	
					2h					
		Bupropion								
		is								
		primarily								
		metabolis								
		ed by								
		CYP2B6.								
		Concurrent								
		administr								
		ation of								
		300101								

 Health Products Regulatory Authority
bupropion bupropion
with
repeated
doses of
ritonavir is
expected
to
decrease
bupropion levels.
These
effects are
thought
to
represent
induction
of I I I I I I I I I I I I I I I I I I I
bupropion
metabolis
m.
However,
because
ritonavir IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
has also
been de la d
shown to
inhibit
CYP2B6 in
vitro, the
recomme
nded
dose of
bupropion bupropion
should
not be
exceeded.
contrast
to
long-term
administr
ation of
ritonavir,
there was
no
significant
interaction
with
bupropion
after
short-term
administr
ation of
low doses
of ritensuir
ritonavir
(200 mg
twice

·		Health Proc	lucts R	egula	tory A	uthority				
		daily for 2								
		days),								
		suggesting								
		<u>9</u> 99								
		reductions								
		in								
		bupropion								
		concentra								
		tions may								
		have								
		onset								
		several								
		days after								
		initiation								
		of								
		ritonavir								
		coadminis								
		tration.								
Steroids		- •								$\vdash$
						<u> </u>			I	⊢┤
Inhaled,										
injectable or										
intranasal										
fluticasone										
propionate,										
budesonide,										
triamcinolon										
e										
		Systemic								
		corticoste								
		roid								
		effects								
		including								
		Cushing's								
		syndrome								
		and								
		adrenal								
		suppressi								
		on								
		(plasma								
		cortisol								
		levels								
		were								
		noted to								
		be								
		decreased								
		86% in								
		the above								
		study)								
		have been								
		reported								
		in patients								
		receiving								
		ritonavir								
		and								
		inhaled or								
1	1	intranasal								
		<i>a</i> .								. 1
		fluticasone								
		fluticasone propionat								

		Health Proc	lucts R	egulat	ory A	uthority		 	 
		e; similar							
		effects							
		could also							
		occur with							
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Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine or nefazodone. The possibility of medicinal product interaction cannot be excluded.

In addition to the interactions listed above, as ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medicinal products should be considered.

# Ritonavir dosed as a pharmacokinetic enhancer

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

<u>Proton pump inhibitors and  $H_2$ -receptor antagonists</u>: proton pump inhibitors and  $H_2$ -receptor antagonists (e.g. omeprazole or ranitidine) may reduce concentrations for co-administered

protease inhibitors. For specific information regarding the impact of coadministration of acid reducing agents, refer to the Summary of Product Characteristics of the co-administered protease inhibitor.Based on interaction studies with the ritonavir boosted protease inhibitors (lopinavir/ritonavir, atazanavir), concurrent administration of omeprazole or ranitidine does not significantly modify ritonavir efficacy as a pharmacokinetic enhancer despite a slight change of exposure (about 6 - 18%).

# 4.6 Fertility, pregnancy and lactation

#### **Pregnancy**

A large amount (6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other protease inhibitors. These data indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Animal data have shown reproductive toxicity (see section 5.3). Ritonavir tablets can be used during pregnancy if clinically needed.

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

## Breastfeeding

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

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

## **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 betaken into account when driving or using machinery.

#### 4.8 Undesirable effects

## <u>Summary of the safety profile</u> Ritonavir dosed as a pharmacokinetic enhancer

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

Ritonavir dosed as an antiretroviral agent

# Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhoea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paraesthesia and oral paraesthesia) and fatigue/asthenia.

#### Tabulated list of adverse reactions

The following adverse reactions of moderate to severe intensity with possible or probable relationship to ritonavir have been reported. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to < 1/10); uncommon ( $\geq 1/1000$  to < 1/100); rare ( $\geq 1/10,000$  to < 1/1,000); not known (cannot be estimated from the available data).

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

Adversereactions in clinical studies and post-marketing in adultpatients		
SystemOrder Class	Frequency	Adverse reaction
Blood and lymphatic system	Common	Decreased white blood cells, decreased haemoglobin,
disorders		decreased neutrophils, increased eosinophils,

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	Uncommon	thrombocytopenia
	oncommon	Increased neutrophils
	Common	Hypersensitivity, including urticaria and face oedema
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Common Uncommon Rare	Hypercholesterolaemia, hypertriglyceridaemia, gout, oedema and peripheral oedema, dehydration (usually associated with gastrointestinal symptoms) Diabetes mellitus Hyperglycaemia
Nervous system disorders	Very common	Dysgeusia, oral and peripheral paresthesia, headache, dizziness, peripheral neuropathy
	Common	Insomnia, anxiety, confusion, disturbance in attention, syncope, seizure
Eye disorders	Common	Blurred vision
Cardiac disorders	Uncommon	Myocardial infarction
Vascular disorders	Common	Hypertension, hypotension including orthostatic hypotension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Very common	Pharyngitis, oropharyngeal pain, cough
Gastrointestinal disorders	Very common Common	Abdominal pain (upper and lower), nausea, diarrhoea (including severe with electrolyte imbalance), vomiting, dyspepsia Anorexia, flatulence, mouth ulcer, gastrointestinal haemorrhage, gastroesophageal reflux disease, pancreatitis
Hepatobiliary disorders	Common	Hepatitis (including increased AST, ALT, GGT), blood bilirubin increased (including jaundice)
Skin and subcutaneous tissue disorders	Very common Common Rare	Pruritus, rash (including erythematous and maculopapular) Acne Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very common Common	Arthralgia and back pain Myositis, rhabdomyolysis, myalgia, myopathy/CPK increased
Renal and urinary disorders	Common	Increased urination, renal impairment (e.g. oliguria, elevated creatinine)
-	Uncommon Not known	Acute renal failure Nephrolithiasis
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Very common Common	Fatigue including asthenia, flushing, feeling hot Fever, weight loss
Investigations	Common Uncommon	Increased amylase, decreased free and total thyroxin Increased glucose, increased magnesium, increased alkaline phosphatase

#### Description of selected adverse reactions

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals.

# Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and can occur many months after initiation of treatment (see section 4.4).

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

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

### Paediatric populations

The safety profile of Ritonavir in children 2 years of age and older is similar to that seen in adults.

## Reportingof suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

# 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

# Ritonavir dosed as a pharmacokinetic enhancer

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

# Ritonavir dosed as an antiretroviral agent

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

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

# Effects on the Electrocardiogram

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

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

#### **Resistance**

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

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

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

# <u>Adult Use</u>

A controlled study completed in 1996 with ritonavir as add-on therapy in HIV-1 infected patients extensively pre-treated with nucleoside analogues and baseline CD4 cell counts  $\leq$  100 cells/µl showed a reduction in mortality and AIDS defining events. The mean average change from baseline over 16 weeks for HIV RNA levels was -0.79 log<sub>10</sub> (maximum mean decrease: 1.29 log<sub>10</sub>) in the ritonavir group versus - 0.01 log10 in the control group. The most frequently used nucleosides in this study were zidovudine, stavudine, didanosine and zalcitabine.

In a study completed in 1996 recruiting less advanced HIV-1 infected patients (CD4 200-500 cells/ $\mu$  l) without previous antiretroviral therapy, ritonavir in combination with zidovudine or alone reduced viral load in plasma and increased CD4 count. The mean average change from baseline over 48 weeks for HIV RNA levels was -0.88 log<sub>10</sub> in the ritonavir group versus -0.66 log10 in the ritonavir + zidovudine group versus -0.42 log<sub>10</sub> in the zidovudine group.

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

# <u>Paediatric Use</u>

In an open label trial completed in 1998 in HIV infected, clinically stable children there was a significant difference (p = 0.03) in the detectable RNA levels in favour of a triple regimen (ritonavir, zidovudine and lamivudine) following 48 weeks treatment.

In a study completed in 2003, 50 HIV-1 infected, protease inhibitor and lamivudine naïve children age 4 weeks to 2 years received ritonavir 350 or 450 mg/m<sup>2</sup> every 12 hours co- administered with zidovudine 160 mg/m<sup>2</sup> every 8 hours and

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lamivudine 4 mg/kg every 12 hours. In intent to treat analyses, 72% and 36% of patients achieved reduction in plasma HIV-1 RNA of  $\leq$  400 copies/ml at Week 16 and 104, respectively. Response was similar in both dosing regimens and across patient age.

In a study completed in 2000, 76 HIV-1 infected children aged 6 months to 12 years who were protease inhibitor naive and naive to lamivudine and/or stavudine received ritonavir 350 or 450 mg/m<sup>2</sup> every 12 hours co-administered with lamivudine and stavudine. In intent to treat analyses, 50% and 57% of patients in the 350 and 450 mg/m<sup>2</sup> dose groups, respectively, achieved reduction in plasma HIV-1 RNA to  $\leq$  400 copies/ml at Week 48.

## 5.2 Pharmacokinetic properties

## <u>Absorption</u>

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV-infected adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough

concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks. The time to maximum concentration (Tmax) remained constant at approximately 4 hours with increasing dose. Renal clearance averaged less than 0.1 l/h and was relatively constant throughout the dosage range.

The pharmacokinetic parameters observed with various dosing schemes of ritonavir alone are shown in the table below. Plasma concentrations of ritonavir after administration of a single 100 mg dose tablet are similar to the 100 mg soft gelatine capsule under fed conditions.

<b>Ritonavir Dosing Regimen</b>					
	100 mg once daily	100 mg twice daily <sup>1</sup>	200 mg once daily	200 mg twice daily	600 mg twice daily
C <sub>max</sub> (µg/ml)	0.84 ± 0.39	0.89	3.4 ± 1.3	4.5 ± 1.3	11.2 ± 3.6
C <sub>trough</sub> (µg/ml)	0.08 ± 0.04	0.22	0.16 ± 0.10	0.6 ± 0.2	3.7 ± 2.6
AUC <sub>12 or 24</sub> (μg·h/ml)	6.6 ± 2.4	6.2	20.0 ± 5.6	21.92 ± 6.48	77.5 ± 31.5
t <sub>1/2</sub> (h)	~5	~5	~4	~8	~3 to 5
Cl/F (L/h)	17.2 ± 6.6	16.1	10.8 ± 3.1	10.0 ± 3.2	8.8 ± 3.2

<sup>1</sup>Values expressed as geometric means. Note: ritonavir was dosed after a meal for all listed regimens.

#### Effects of food on oral absorption

Food slightly decreases the bioavailability of the ritonavir film-coated tablets. Administration of a single 100 mg dose of ritonavir film-coated tablets 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 Cmax.

# **Distribution**

The apparent volume of distribution (VB/F) of ritonavir is approximately 20 - 40 l after a single 600 mg dose. The protein binding of ritonavir in human plasma is approximately 98 - 99% and is constant over the concentration range of  $1.0 - 100 \mu g$  /ml. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities.

Tissue distribution studies with <sup>14</sup>C-labelled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of ritonavir. Tissue to plasma ratios of approximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

# **Biotransformation**

Ritonavir was noted to be extensively metabolised by the hepatic cytochrome P450 system, primarily by the CYP3A isozyme family and to a lesser extent by the CYP2D6 isoform. Animal studies as well as in vitro experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent compound. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent compound.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors and other products metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir (see section 4.5).

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# **Elimination**

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

# **Special Pppulations**

No clinically significant differences in AUC or  $C_{max}$  were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass. Ritonavir plasma exposures in patients 50 – 70 years of age when dosed 100 mg in combination with lopinavir or at higher doses in the absence of other protease inhibitors is similar to that observed in younger adults.

## Patients with impaired liver function

After multiple dosing of ritonavir to healthy volunteers (500 mg twice daily) and subjects with mild to moderate hepatic impairment (Child Pugh Class A and B, 400 mg twice daily) exposure to ritonavir after dose normalisation was not significantly different between the two groups.

## Patients with impaired renal function

Ritonavir pharmacokinetic parameters have not been studied in patients with renal impairment. However, since the renal clearance of ritonavir is negligible, no changes in the total body clearance are expected in patients with renal impairment.

## **Paediatricpatients**

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

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

# 5.3 Preclinical safety data

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocyti celements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and protein urea were noted in rats and are feltto be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

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

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

Longterm 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

<u>Tablet:</u> Copovidone Sorbitan laureate (E493) Silica, colloidal anhydrous (E551) Calcium Hydrogen Phosphate, anhydrous Sodium stearyl fumarate

<u>Film-coating:</u> Hypromellose (E464) Titanium dioxide (E171) Macrogol Hydroxypropyl cellulose (E463) Talc (E553b) Silica, colloidal anhydrous (E551) Polysorbate 80 (E433)

# 6.2 Incompatibilities

Not applicable.

# 6.3 Shelf life

Blister pack: 24 months Bottle pack: 3 years. After first opening the bottle: 120 days

# 6.4 Special precautions for storage

Store below 25°C.

# 6.5 Nature and contents of container

Ritonavir Tablets are packed in white high density polyethylene (HDPE) bottles closed with white child resistant (screw cap) polypropylene caps and Alu-Alu blister pack.

Pack sizes: HDPE bottle pack: 30, 90 and 120 tablets. Blister pack: 30x1, 90x1 and 120x1 tablets.

Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal

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

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## **7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Ireland Ltd. Euro House Euro Business Park Little Island Cork T45 K857 Ireland

# **8 MARKETING AUTHORISATION NUMBER**

PA2315/176/001

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7<sup>th</sup> April 2017 Date of last renewal: 8<sup>th</sup> October 2020

## **10 DATE OF REVISION OF THE TEXT**

March 2024