For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Ritonavir Capsules (100 mg)

Ritomune-100

Warning
CO-ADMINISTRATION OF **RITOMUNE-100** WITH CERTAIN NONSEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTIARRHYTHMICS, OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF **RITOMUNE-100** ON THE HEPATIC METABOLISM OF CERTAIN DRUGS. SEE CONTRAINDICATIONS AND PRECAUTIONS SECTIONS.

Composition

Ritonavir Capsules
Each soft gelatin capsule contains
Ritonavir ..... 100 mg

Description

Ritomune-100 is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV).

Indications

Ritomune-100 is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

Dosage and Administration

It is recommended that **Ritomune-100** be taken with meals if possible.

Adults

The recommended dosage of ritonavir is 600 mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. If saquinavir and ritonavir are used in combination, the dosage of saquinavir should be reduced to 400 mg twice daily. The optimum dosage of ritonavir (400 mg or 600 mg twice daily), in combination with saquinavir, has not been determined; however, the combination regimen was better tolerated in patients who received ritonavir 400 mg twice daily.

General Dosing Guidelines

Patients should be aware that frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paraesthesias, may diminish as therapy is continued. In addition, patients initiating combination regimens with **Ritomune-100** and nucleosides may improve gastrointestinal tolerance by initiating **Ritomune-100** alone and subsequently adding nucleosides before completing two weeks of **Ritomune-100** monotherapy.

Contraindications

Ritomune-100 is contraindicated in patients with known hypersensitivity to ritonavir or any of its ingredients.
Ritomune-100 should not be administered concurrently with the drugs listed in Table 1 because competition for primarily CYP3A by ritonavir could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression.
Postmarketing reports indicate that co-administration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities.

Table 1: Drugs that are contraindicated with ritonavir use

Drug Class	Drugs Within Class that are Contraindicated with Ritonavir
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Antimigraine	Dihydroergotamine, ergotamine
Sedative/hypnotics	Midazolam, triazolam
GI motility agent	Cisapride
Neuroleptic	Pimozide

Warnings and Precautions

Drug Interactions

The magnitute of the interactions and therapeutic consequences between ritonavir and the drugs listed in Table 2 cannot be predicted with any certainty. When co-administering ritonavir with any agent listed in Table 2 special attention is warranted.

Cardiac and neurologic events have been reported with ritonavir when co-administered with disopyramide, mexiletine, nefazodone, fluoxetine and beta blockers. The possibility of drug interaction cannot be excluded. Particular caution should be used when prescribing sildenafil in patients receiving ritonavir. Co-administration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection

Concomitant use of ritonavir with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including ritonavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (eg atorvastatin or cerivastatin) The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including ritonavir are used in combination with these drugs.

Concomitant use of ritonavir and St Johns wort (*Hypericum perforatum*) or products containing St Johns wort is not recommended. Coadministration of protease inhibitors including ritonavir with St Johns wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of ritonavir and lead to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.

Table 2: Predicted drug interactions: Use with caution, dose decrease of coadministered drug may be needed

Drug Class	Examples of Drugs whose Plasma Concentrations May Be Decreased by Co-Administration with Ritonavir
Analgesics, narcotic	Tramadol, propoxyphene
Antiarrhythmics	Disopyramide, lidocaine, mexilitine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antidepressants	Bupropion, nefazodone, selective serotonin reuptake inhibitor (SSRIs), tricyclics
Antiemetics	Dronabinol
Antiparasitics	Quinine
beta-blockers	Metoprolol, timolol
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Hypolipidemics, HMG CoA reductase inhibitors	Atorvastatin, cerivastatin, lovastatin, simvastatin
Immunosuppressants	Cyclosporine, tacrolimus
Neuroleptics	Perphenazine, risperidone, thioridazine
Sedative/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, zolpidem
Steroids	Dexamethasone, prednisone
Stimulants	Methamphetamine
Coadministration with lovastatin and simvastatin is not recommended (see Warnings and Precautions)	
Anticoagulants	Warfarin
Anticonvulsants	Phenytoin, divalproex, lamotrigine
Antiparasitics	Atovaquone

Concomitant use of ritonavir with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including ritonavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g. atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including ritonavir, are used in combination with these drugs.

Concomitant use of ritonavir and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including ritonavir, with St.John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of ritonavir and lead to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.

Allergic Reactions

Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Rare cases of anaphylaxis and Stevens-Johnson syndrome have also been reported.

Hepatic Reactions

Hepatic transaminases elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminases elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Increased AST/ALT monitoring should be considered in these patients, especially during the first three months of ritonavir treatment.

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS.

Pancreatitis

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 increased risk of elevated triglycerides and pancreatitis.

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

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

General

Ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function..

Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Disorders

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

Laboratory Tests

Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating ritonavir therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information concerning laboratory test alterations associated with nucleoside analogues, physicians should refer to the complete product information for each of these drugs.

Pregnancy

Category B. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ritonavir is administered to a nursing woman. However, it is advised that HIV-infected women do not breast-feed to avoid postnatal transmission of HIV to a child who may not be infected.

Paediatric use

The safety and pharmacokinetic profile of ritonavir in paediatric patients below the age of 2 years have not been established. In HIV-infected patients aged 2 to 16 years, the adverse event profile appears to be similar to that for adult patients.

Side effects

Overall the most frequently reported clinical adverse events, other than asthemia, among patients receiving ritonavir were gastrointestinal and neurological disturbances including nausea, diarrhoea, vomiting, anorexia, abdominal pain, taste perversion, and circumoral and peripheral paraesthesias.

Adverse events occurring in less than 2% of patients receiving ritonavir in all phase II/phase III studies and considered at least possibly related and of at least moderate intensity are as follows:

*Body as a Whole:*Abdominal pain, asthenia, fever, headache, malaise, pain (unspecified)

Cardiovascular: Syncope, vasodilation

Digestive: Anorexia, constipation, diarrhea, dyspepsia, fecal, incontinence, flatulence, local throat irritation, nausea, vomiting

Metabolic and Nutritional: *Weight loss*

Musculoskeletal: Arthralgia, myalgia

Nervous: Anxiety, circumoral paresthesia, confusion, depression, dizziness, insomnia, paresthesia, peripheral paresthesia, somnolence, thinking abnormal

Respiratory: Pharyngitis

Skin and Appendages: Rash, sweating

Special senses: Taste perversion

Urogential: Nocturia

Laboratory Abnormalities: Elevations in cholesterol, triglycerides, SGOT and SGPT have been reported.

Overdosage

Acute Overdosage

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

The approximate lethal dose was found to be greater than 20 times the related human dose in rats and 10 times the related human dose in mice.

Management of Overdosage

Treatment of overdose with ritonavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

Presentation

Ritomune-100

Bottle of 84 capsules
Container of 60 capsules.

Cipla

250M I JPA-2