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RITOVIR
(Ritonavir Tablets 100 mg)
2080363

Name of the product
RITOVIR (Ritonavir Tablets 100 mg)

Name and strength of Active Ingredient
Name : Ritonavir
Strength : 100 mg

Dosage form
Oral

Product Description
Ritonavir Tablets 100 mg
White to off white, capsule shaped, film coated tablets debossed with 'H' on one side and 'R9' on other side.

PHARMACOLOGY

Pharmacodynamics:

Mechanism of Action
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.

Pharmacokinetics
Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults.

About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

Indications
Ritonavir is indicated alone or in combination with other antiretroviral agents for the treatment of patients with HIV infection when therapy is warranted based on clinical and/or immunological evidence of disease progression.

Recommended dose
Ritonavir tablets are administered orally and should preferably be given with food.

Adults
The recommended dose of ritonavir tablets is 600 mg (six tablets) twice daily by mouth and should be given with food. Ritonavir tablets should be swallowed whole and not chewed, broken or crushed. Use of a dose titration schedule may help to reduce treatment emergent adverse event while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300mg twice daily for a period of three days and increased by 100 mg twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should be aware that frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paresthesias, may diminish as therapy is continued. Patients should not remain on 300 mg twice daily for more than three days.

Dual PI Containing Combination Regimens
Clinical experience with dual therapy including therapeutic doses of ritonavir with another protease inhibitor is limited. Ritonavir extensively inhibits the metabolism of most available protease inhibitors. Hence, any consideration of dual therapy with ritonavir should take into account the pharmacokinetic interaction and safety data of involved agents. There is extensive cross-resistance in this class of agents. The combination of two PIs with the least overlapping patterns of resistance should be considered. The use of ritonavir in such regimens should be guided by these factors. For the use of ritonavir with saquinavir a cautious titration of the dose has been used by initiating ritonavir dosing at 300 mg twice daily. For the use of ritonavir with indinavir a cautious titration of the dose has been used by initiating ritonavir dosing at 200 mg twice daily increasing by 100 mg twice daily reaching 400 mg twice daily within two weeks.

Mode of administration
Ritonavir is administered orally. Ritonavir tablets should be swallowed whole, and not chewed, broken or crushed. Take Ritonavir with meal.

Contraindications
Ritonavir is contraindicated in patients with known hypersensitivity to ritonavir or any of its formulation excipients. Co-administration of ritonavir is contraindicated with the drugs listed in Table 1:

Table 1 Drugs that are Contraindicated with Ritonavir

Drug Class	Drugs within Class that are Contraindicated with	Clinical Comments
Alpha1-adrenoreceptor antagonist	alfuzosin HCL	Potential for hypotension
Antiarrhythmics	amiodarone, bepridil, flecainide, propafenone, quinidine, encainide	Potential for cardiac arrhythmias.
Antifungal	voriconazole	Significant decreases in voriconazole plasma concentrations may lead to loss of antifungal response.
Antihistamines	astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine, thereby, increasing the risk of serious arrhythmias from these agents
Antipsychotic	blonanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonaserin.
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia have been associated with coadministration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
GI Motility Agent	cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's wort (hypericum perforatum)	Co-administration may lead to a decrease in ritonavir levels and to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Long acting betaadrenoceptor agonist	salmeterol	May result in potential increased risk of cardiovascular adverse events associated with salmeterol.
Neuroleptic	pimozide	Potential for cardiac arrhythmias.
PDE5 inhibitor	sildenafil	*only when used for the treatment of pulmonary arterial hypertension (PAH). Increased potential for sildenafil associated adverse events (which include hypotension and syncope).
Sedative/hypnotics	midazolam, triazolam	Ritonavir is likely to produce large increases in these highly metabolized sedatives and hypnotics resulting in the potential for prolonged or increased sedation or respiratory depression.

*see Warnings and Precautions and Drug Interactions for coadministration of sildenafil in patients with erectile dysfunction

Warnings and precautions
When co-administering Ritonavir with other protease inhibitors. 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.

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

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.

Laboratory tests: Ritonavir has been associated with alterations in triglycerides, cholesterol, SGOT, SGPT, GGT, CPK and uric acid. Appropriate laboratory testing should be performed prior to initiating Ritovir therapy and at periodic intervals or if any clnical signs or symptoms occur during therapy.

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 post marketing 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 these patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases.

Consideration should be given to the monitoring of blood glucose.

PR Interval Prolongation
Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare reports of second or third degree atrioventricular block in patients with underlying structural heart disease and preexisting conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir. Ritonavir should be used with caution in such patients.

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.

Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including ritonavir. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jiroveci pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

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

Interaction with other Medicaments
When co-administering ritonavir with other protease inhibitors, see the full prescribing information for that protease inhibitor including information for drug interactions

Effects On Ritonavir
Agents which increase CYP3A activity (e.g., phenobarbital, carbamazepine, dexamethasone, phenytoin, rifampin and rifabutin) would be expected to increase the clearance of ritonavir resulting in decreased ritonavir plasma concentrations.
Tobacco use is associated with a decrease in the AUC of ritonavir.

Effects On Coadministered Drugs
Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9 > CYP2C19 >> CYP2A6, CYP1A2, CYP2E1.

There is evidence that ritonavir may induce glucuronosyl transferase, CYP1A2, CYP2C9, and CYP2C19 enzymes; thus, decreased plasma concentrations of the other drug and loss of therapeutic effects during ritonavir co-administration may signify the need for dosage alteration of these agents. Co-administration of ritonavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects. Careful monitoring of therapeutic and adverse effects is recommended when these drugs are concomitantly administered with ritonavir. Dosage reductions may be required for those agents extensively metabolized by CYP3A. Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine, nefazodone, or fluoxetine. The possibility of drug interaction cannot be excluded.

Alprazolam: Coadministration of alprazolam with ritonavir resulted in a statistically significant decrease in mean alprazolam Cmax values but not in mean AUC values. Similarly, a statistically significant effect was observed on the sedation effect curve but not on the extent of sedation. Mild psychomotor impairment was confounded by a learning effect. These pharmacokinetic and pharmacodynamic results are inconsistent when considering the pharmacologic effect of alprazolam. These results were not considered clinically significant.

Amprenavir: Literature reports have shown that concentrations of the HIV-protease inhibitor, amprenavir, are increased when co-administered with ritonavir.

Anticancer Agents (dasatinib, nilotinib, vincristine, vinblastine): Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.

Dimensions	210 x 350 mm (Book Fold: 35 x 35 mm)
Customer/Country	Camber / Malaysia
Spec	Bible Paper 40 GSM
Pantone Colours	Black
Version No.	03

Note: Pharma Code, Material Code and Product Name Orientation will be change based on Machine folding feasibility at vendor.

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Bedaquiline: Bedaquiline must be used cautiously with ritonavir, only if the benefit of co-administration outweighs the risk.

Bosentan: Co-administration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (Cmax) and area-under-thecurve (AUC). Refer to the bosentan label for prescribing information.

Bupropion: Bupropion is primarily metabolized by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels.

Buspirone: Buspirone is primarily metabolized by CYP3A4. Concurrent administration of buspirone with drugs that potently inhibit CYP3A, such as ritonavir is expected to substantially elevate buspirone levels. When co-administered with ritonavir, a dose reduction or low dose of buspirone used cautiously is recommended.

Clarithromycin: Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Colchicine: Concentrations of colchicine are expected to increase when coadministered with ritonavir. Refer to the colchicine label for prescribing information.

Delavirdine: Delavirdine is an inhibitor of CYP3A-mediated metabolism. When used in combination with delavirdine, a dose reduction of ritonavir should be considered.

Desipramine: Dosage reduction of desipramine should be considered in patients taking the combination.

Didanosine: Dose alteration of ddI during concomitant ritonavir therapy should not be necessary; however, dosing of the two drugs should be separated by 2.5 hours to avoid formulation incompatibility.

Digoxin: Caution should be exercised when coadministering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Fentanyl: Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.

Fluticasone propionate: 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. Consider alternatives to fluticasone propionate or budesonide, particularly for longterm use.

Fusidic Acid: Coadministration of protease inhibitors, including ritonavir with fusidic acid is expected to increase fusidic acid, as well as the protease inhibitor concentration in plasma.

Hypericum perforatum (St. John's Wort): Patients on ritonavir should not use concomitantly products containing St. John's Wort (Hypericum perforatum) since it may be expected to result

in reduced plasma concentrations of ritonavir. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance.

Indinavir: Ritonavir inhibits the CYP3A-mediated metabolism of indinavir. Coadministration of ritonavir with indinavir will result in increased indinavir serum concentrations. There are limited safety or efficacy data available on the use of this combination in patients. The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted.

Ketoconazole: No dosage adjustment of ritonavir is necessary; however, doses of ketoconazole 200 mg/day or greater should be used with caution in combination with ritonavir and a decreased dosage of ketoconazole may be considered.

Maraviroc: Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with ritonavir. For further details see complete prescribing information for maraviroc.

Methadone: Coadministration of ritonavir with methadone is expected to decrease methadone concentrations. A dosage increase of methadone may be considered.

Nelfinavir: Interactions between ritonavir and nelfinavir are likely to involve both cytochrome P450 inhibition and induction. Concurrent ritonavir 400 mg twice daily significantly increases the concentrations of M8 (the major active metabolite of nelfinavir), and results in a smaller increase in nelfinavir concentrations.

Oral Contraceptives or Patch Contraceptives: Increased doses of oral contraceptives or patch contraceptives containing ethinyl estradiol, or alternate methods of contraception, should be considered.

Quetiapine: Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Refer to quetiapine prescribing information for dosing instructions.

Rifabutin: Concomitant administration of ritonavir and rifabutin resulted in an increase in the AUC of rifabutin and its active metabolite 25-O-deacetyl rifabutin, respectively. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (e.g., 150 mg every other day or three times a week). Further dosage reduction may be necessary.

Rivaroxaban: coadministration of ritonavir and rivaroxaban resulted in increased exposure of rivaroxaban which may lead to risk of increased bleeding.

Saquinavir: Saquinavir and ritonavir should not be given together with rifampicin due to risk of severe hepatotoxicity (presenting as increased transaminases) if the three drugs are given together.

Simeprevir: It is not recommended to co-administer ritonavir with simeprevir.

PDE5 inhibitors:

Avanafil: Co-administration of ritonavir with avanafil is not recommended.

Sildenafil: Coadministration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.

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

Tadalafil: Use tadalafil for the treatment of erectile dysfunction with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events. When tadalafil is used concomitantly with ritonavir in patients with pulmonary arterial hypertension, refer to the tadalafil label for prescribing information.

Vardenafil: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

Theophylline: An increased dosage of theophylline may be required.

Trazodone: Concomitant use of ritonavir and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Voriconazole: Co-administration of Voriconazole and Ritonavir is contraindicated.

Warfarin: The net effect of ritonavir coadministration on the anticoagulant effect of warfarin is difficult to predict based upon these pharmacokinetic results. Initial frequent monitoring of the INR during ritonavir and warfarin coadministration is indicated.

Pregnancy and lactation

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

Use in lactation: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of ritonavir on infant development are not known, ritonavir should be used in nursing women only when the potential benefits clearly outweigh the potential risks. Some health experts recommend that HIV-infected women should not breast feed their infants to avoid transmission of HIV.

Side effects
The following adverse reactions are listed as follows by body system.

Body as a Whole: Enlarged abdomen, accidental injury, allergic reaction, back pain, cachexia, chest pain, chills, facial edema, facial pain, flu syndrome, altered hormone level, hypothermia, kidney pain, neck pain, neck rigidity, pain (unspecified), substernal chest pain and photosensitivity reaction.

Cardiovascular System: Hypotension, migraine, palpitation, peripheral vascular disorder, postural hypotension, syncope and tachycardia.

Digestive System: Abnormal stools, bloody diarrhea, cheilitis, colitis, dry mouth, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, hepatitis, hepatomegaly, ileitis, liver damage, mouth ulcer, pancreatitis, rectal disorder, tenesmus and thirst.

Endocrine System: Diabetes mellitus
Hemic and Lymphatic System: Anemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis and thrombocytopenia.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glycosuria, gout, hypercholesteremia, peripheral edema and weight loss.

Musculoskeletal System: Arthralgia, arthrosis, joint disorder, muscle cramps, muscle weakness, myositis and twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, amnesia, anxiety, aphasia, ataxia, confusion, convulsion, depression, diplopia, emotional lability, euphoria, grand mal convulsion, hallucinations, hyperesthesia, incoordination, decreased libido, nervousness, neuralgia, neuropathy, paralysis, peripheral neuropathy, peripheral sensory neuropathy, personality disorder, tremor, urinary retention and vertigo.

Respiratory System: Asthma, dyspnea, epistaxis, hiccup, hypoventilation, increased cough, interstitial pneumonia, lung disorder and rhinitis.

Skin and Appendages: Acne, contact dermatitis, dry skin, eczema, folliculitis, maculopapular rash, molluscum contagiosum, pruritus, psoriasis, seborrhea, urticaria and vesiculobullous rash.

Special Senses: Abnormal electro-oculogram, abnormal electroretinogram, abnormal vision, amblyopia/ blurred vision, blepharitis, ear pain, eye pain, hearing impairment, increased cerumen, iritis, parosmia, photophobia, taste loss, tinnitus, uveitis and visual field defect.

Urogenital System: Dysuria, hematuria, impotence, kidney calculus, kidney failure, nocturia, penis disorder, polyuria, urethritis and urinary frequency.

Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.

Symptoms and treatment of overdose
Human experience of acute overdose with ritonavir is limited. One patient was reported taking 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 with ritonavir overdose.

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

Storage condition
Store below 30°C and protect from moisture. Store in original container.

Dosage forms and packaging available
30 Tablets in HDPE container

Product Registration holder:
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