| 597-2023-02 | 10684 Ritonavir Tablets, USP | 2072166 | 2D | | |
|---|--|--|---|--|--|
| HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use RITONAVIR TABLETS safely and effectively. See full prescribing information for RITONAVIR TABLETS. RITONAVIR TABLETS. RITONAVIR tablets, for oral use Initial U.S. Approval: 1996 WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS See full prescribing information for complete boxed warning Co-administration of ritonavir with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing intonavir or when prescribing other medications to patients already taking ritonavir. (4, 5.1) INDICATIONS AND USAGE | Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations (5.3, 8.6) Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate (5.4) Allergic Reactions/Hypersensitivity: Allergic reactions have been reported and include anaphylaxis, toxic epidermal necrolysis, Stevens-Johnson syndrome, bronchospasm and angioedema. Discontinue treatment if severe reactions develop (5.5, 6.2) PR interval prolongation may occur in some patients. Cases of second and third degree heart block have been reported. Use with caution with patients with preexisting conduction system disease, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administering with other drugs that may prolong the PR interval (5.6, 12.3) Total cholesterol and triglycerides elevations: Monitor prior to therapy and periodically thereafter (5.7) Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.8) Patients may develop redistribution/accumulation of body fat (5.10) Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required (5.11) | prescribing information for that pro 7.1 Potential for Ritonavir to Ritonavir is an inhibitor of cytochro Agents that are extensively metab (greater than 3-fold) when co-adm and for which elevated plasma cor other CYP3A substrates may requir Ritonavir also inhibits CYP2D6 to a | as been reported. with other protease inhibitor including in Affect Other Drugs me P450 3A (CYP3A) and olized by CYP3A and have inistered with ritonavir. To centrations are associate te a dose adjustment or add a lesser extent. Co-adminis | itors (atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir), see the full portant information for drug interactions. high first pass metabolism appear to be the most susceptible to large increases in AUC hus, co-administration of ritonavir with drugs highly dependent on CYP3A for clearance d with serious and/or life-threatening events is contraindicated. Co-administration with litional monitoring as shown in Table 4. | Patient Information Ritonavir Tablets (rih-TON-ah-veer) What is the most important information I should know about ritonavir? • Ritonavir can interact with other medicines and cause serious side effects. It important to know the medicines that should not be taken with ritonavir. See the section "Who should not take ritonavir?" |
| Ritonavir tablets are HIV protease inhibitors indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1) | The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. DRUG INTERACTIONS | and CYP2B6 as well as other enzym These examples are a guide and nu should consult appropriate reference 7.2 Established and Other Por Table 4 provides a list of establishe | nes, including glucuronosyl ot considered a comprehe ces for comprehensive info tentially Significant Dru ed or potentially clinically s | nsive list of all possible drugs that may interact with ritonavir. The healthcare provider rmation. | What is ritonavir? Ritonavir tablets are prescription medicines that are used with other antivir medicines to treat people with human immunodeficiency virus (HIV-1) infection. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). |
| DOSAGE FORMS AND STRENGTHS Tablet: 100 mg (3) CONTRAINDICATIONS Ritonavir is contraindicated in patients with known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome) | and during therapy (4, 5.1, 7, 12.3) USE IN SPECIFIC POPULATIONS Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission (8.2). See 17 for PATIENT COUNSELING INFORMATION and FDA- approved patient labeling. | Table 4. Established and Other P Concomitant Drug Class: Drug Name | Potentially Significant D Effect on Concentration of | rug Interactions Clinical Comment | Do not take ritonavir if you or your child: are allergic to ritonavir or any of the ingredients in ritonavir. See the end of t leaflet for a complete list of ingredients in ritonavir. |
| or any of its ingredients (4) Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events (4) Co-administration with drugs that significantly reduce ritonavir (4) | Revised: 02/2023 | HIV-Antiviral Agents | Ritonavir or Concomitant Drug ↑ amprenavir | See the complete prescribing information for fosamprenavir, atazanavir, | If you take any of the following medicines: alfuzosin |
| The following have been observed in patients receiving ritonavir: The following have been observed in patients receiving ritonavir: The concomitant use of ritonavir and certain other drugs may result in known or potentially significant drug interactions. Consult the full | | atazanavir darunavir fosamprenavir HIV-1 Protease Inhibitor: | ↑ atazanavir ↑ darunavir ↑ indinavir | darunavir for details on co-administration with ritonavir. Appropriate doses for this combination, with respect to efficacy and safety, | apalutamide ranolazine |
| The concontraint use of international and certain during image may result in known or potentianty significant drug interactions. Consult the fun prescribing information prior to and during treatment for potential drug interactions. (5.1, 7.2) Toxicity in preterm neonates: Ritonavir oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of ritonavir oral solution in this patient population has not been established (2.4, 5.2) | | indinavir HIV-1 Protease Inhibitor: saquinavir | ↑ saquinavir | have not been established. See the complete prescribing information for saquinavir for details on co- administration of saquinavir and ritonavir. Saquinavir/ritonavir in combination with rifampin is not recommended due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if | dronedarone colchicine, if you have kidney or liver problems. lurasidone |
| FULL PRESCRIBING INFORMATION: CONTENTS* | 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy | HIV-1 Protease Inhibitor: | ↑ tipranavir | the three drugs are given together. See the complete prescribing information for tipranavir for details on co- | pimozide amiodarone |
| WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING Reactions 1 indications and usage | 8.2 Lactation 8.3 Females and Males of Reproductive Potential | tipranavir Non-Nucleoside Reverse | ↑ ritonavir | administration of tipranavir and ritonavir. Appropriate doses of this combination with respect to safety and efficacy have | ergot-containing medicines including: |
| 2 DOSAGE AND ADMINISTRATION 2.1 General Administration Recommendations | 8.4 Pediatric Use 8.5 Geriatric Use 8.6 Hepatic Impairment | Transcriptase Inhibitor: delavirdine HIV-1 CCR5 – antagonist: | ↑ maraviroc | not been established. See the complete prescribing information for maraviroc for details on co- | dihydroergotamine mesylate ergotamine tartrate |
| 2.3 Dosage Recommendations in Pediatric Patients | 10 OVERDOSAGE | maraviroc Integrase Inhibitor: | ↓ raltegravir | administration of maraviroc and ritonavir-containing protease inhibitors. The effects of ritonavir on raltegravir with ritonavir dosage regimens greater | methylergonovine maleate |
| 2.6 Dose Modification due to Drug Interaction DOSAGE FORMS AND STRENGTHS | 11 DESCRIPTION 12 Clinical Pharmacology | raltegravir | | than 100 mg twice daily have not been evaluated, however raltegravir concentrations may be decreased with ritonavir coadministration. | cisapride flecainide |
| 4 CONTRAINDICATIONS | 12.1 Mechanism of Action 12.2 Pharmacodynamics | Other Agents Alpha 1- | ↑ alfuzosin | Contraindicated due to potential hypotension <i>(see Contraindications (4))</i> . | o lovastatin |
| 5 WARNINGS AND PRECAUTIONS 5.1 Risk of Serious Adverse Reactions Due to Drug Interactions | 12.3 Pharmacokinetics 12.4 Microbiology | Adrenoreceptor Antagonist: | 1 | | o simvastatin |
| 5.2 Toxicity in Preterm Neonates 5.3 Hepatotoxicity 5.4 Pancreatitis | 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility | alfuzosin | | | Iomitapide alidensfil (PEVATIO[®]) only when used for treating the lung problem sylmen |
| 5.4 Pancreatitis 5.5 Allergic Reactions/Hypersensitivity 5.6 PRInterval Prolongation | 14 CLINICAL STUDIES 14.1 Advanced Patients with Prior Antiretroviral Therapy 14.2 Patients without Prior Antiretroviral Therapy | Antianginal: ranolazine | ↑ ranolazine | Contraindicated due to potential for serious and/or life-threatening reactions [see Contraindications (4]]. | sildenafil (REVATIO[®]) only when used for treating the lung problem, pulmon arterial hypertension (PAH) |
| 5.6 Fritinervarronongation 5.7 Lipid Disorders 5.8 Diabetes Mellitus/Hyperglycemia | 14.2 Patients without Prior Antiretroviral Therapy 15 REFERENCES | Analgesics, Narcotic: tramadol, | ↑ analgesics | A dose decrease may be needed for these drugs when co-administered with ritonavir. | \circ triazolam |
| 5.9 Inmune Reconstitution Syndrome 5.10 Fat Redistribution | 16 HOW SUPPLIED/STORAGE AND HANDLING | propoxyphene, methadone, | ↓ methadone | Dosage increase of methadone may be considered. | o midazolam when taken by mouth |
| 5.11 Patients with Hemophilia 5.12 Resistance/Cross-resistance | 17 PATIENT COUNSELING INFORMATION * Sections or subsections omitted from the full prescribing information are not listed. | fentanyl | ↑ ↑ fentanyl | Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administrative units incoming the second se | propafenone guinidine |
| 5.13 Laboratory Tests 6 ADVERSE REACTIONS | | Anesthetic: | ↓ meperidine/ | administered with ritonavir. Dosage increase and long-term use of meperidine with ritonavir are not recomposed due to the increased economications of the metabolite. | quintume St. John's Wort (Hypericum perforatum) or a product that contains St. Joh |
| 6.1 Clinical Trial Experience 6.2 Postmarketing Experience | | meperidine | ↑ normeperidine (metabolite) | recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (a.g., existence) | wort |
| 7 DRUG INTERACTIONS 7.1 Potential for Ritonavir to Affect Other Drugs | | Antialcoholics: | | (e.g., seizures). Ritonavir formulations contain alcohol, which can produce disulfiram-like reactions when an eleministened with disulfiram or other down that produce this | $_{\odot}$ voriconazole if your ritonavir tablets dose is 400 mg every 12 hours or great |
| 7.1 Potential for Kitonawir to Affect Utiner Drugs 7.2 Established and Other Potentially Significant Drug Interactions | | disulfiram/ metronidazole | | reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole). | Serious problems can happen if you or your child takes any of these medicines w |
| | | Antiarrhythmics: amiodarone, | ↑ antiarrhythmics | Contraindicated due to potential for cardiac arrhythmias <i>(see Contraindications (4))</i> . | ritonavir. |
| FULL PRESCRIBING INFORMATION WARNING: DRUG DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS | 5.9 Immune Reconstitution Syndrome Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including ritonavir. During | dronedarone, flecainide, | | | Before taking ritonavir, tell your healthcare provider about all of your medi |
| WARMING: UNGG-UNGG IN TERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR THE THREATENING KEACTIONS Co-administration of ritonavir with several classes of drugs including sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events due to possible effects of ritonavir on the | the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as <i>Mycobacterium avium</i> infection, cytomegalovirus, <i>Pneumocystis jiroveci</i> pneumonia, or tuberculosis), | propafenone, quinidine Antiarrhythmics: | ↑ antiarrhythmics | Caution is warranted and therapeutic concentration monitoring is recommended | conditions, including if you or your child: have liver problems, including Hepatitis B or Hepatitis C |
| preparations may result in potentiarly serious and/or inte-infreatening adverse events oue to possible effects of ritonavir on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing ritonavir or when prescribing other medications to patients already taking ritonavir <i>(see Contraindications (4), Warnings and Precautions (5, 1)).</i> | 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 | disopyramide, lidocaine, mexiletine | | for antiarrhythmics when co-administered with ritonavir, if available. | have heart problems, including hepatitis b of hepatitis c have heart problems |
| 1 INDICATIONS AND USAGE | reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment. 5.10 Fat Redistribution | Anticancer Agents: abemaciclib, | ↑ anticancer agents ↓ ritonavir® | Apalutamide is contraindicated due to potential for loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors <i>(see</i> | • have high blood sugar (diabetes) |
| Ritonavir tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. 2 DOSAGE AND ADMINISTRATION | Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term | apalutamide, dasatinib, | | Contraindications (4)). Avoid co-administration of encorafenib or ivosidenib with ritonavir due to | have bleeding problems or hemophilia are program to plan to become program to |
| | | 1 | 1 | and a standard state of a second state of the | are progrant or plan to become progrant |

encorafenib.

ibrutinib, ivosidenib,

DOSAGE AND ADMINISTRATION General Administration Recommendation 2.1

Ritonavir must be used in combination with other antiretroviral agents

5 11 Patients with Hemonhilia

ces of these events are currently unknown. A causal relationship has not been established

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comment |
|--|---|---|
| HIV-Antiviral Agents | | |
| HIV-1 Protease Inhibitor: atazanavir darunavir fosamprenavir | ↑ amprenavir ↑ atazanavir ↑ darunavir | See the complete prescribing information for fosamprenavir, atazanavir, darunavir for details on co-administration with ritonavir. |
| HIV-1 Protease Inhibitor: indinavir | ↑ indinavir | Appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| HIV-1 Protease Inhibitor: saquinavir | ↑ saquinavir | See the complete prescribing information for saquinavir for details on co- administration of saquinavir and ritonavir. Saquinavir/ritonavir in combination with rifampin is not recommended due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three drugs are given together. |
| HIV-1 Protease Inhibitor: tipranavir | ↑ tipranavir | See the complete prescribing information for tipranavir for details on co- administration of tipranavir and ritonavir. |
| Non-Nucleoside Reverse Transcriptase Inhibitor: delavirdine | ↑ ritonavir | Appropriate doses of this combination with respect to safety and efficacy have not been established. |
| HIV-1 CCR5 – antagonist: maraviroc | ↑ maraviroc | See the complete prescribing information for maraviroc for details on co- administration of maraviroc and ritonavir-containing protease inhibitors. |
| Integrase Inhibitor: raltegravir | ↓ raltegravir | The effects of ritonavir on raltegravir with ritonavir dosage regimens greater than 100 mg twice daily have not been evaluated, however raltegravir concentrations may be decreased with ritonavir coadministration. |
| Other Agents | | |
| Alpha 1- Adrenoreceptor Antagonist: alfuzosin | ↑ alfuzosin | Contraindicated due to potential hypotension <i>[see Contraindications (4)]</i> . |
| Antianginal: ranolazine | ↑ ranolazine | Contraindicated due to potential for serious and/or life-threatening reactions (see Contraindications (4)). |
| Analgesics, Narcotic: tramadol, propoxyphene, | ↑ analgesics | A dose decrease may be needed for these drugs when co-administered with ritonavir. Dosage increase of methadone may be considered. |
| methadone, fentanyl | ↓ methadone ↑ fentanyl | Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir. |
| Anesthetic: meperidine | ↓ meperidine/ ↑ normeperidine (metabolite) | Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures). |
| Antialcoholics: disulfiram/ metronidazole | | Ritonavir formulations contain alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole). |
| Antiarrhythmics: amiodarone, dronedarone, flecainide, propafenone, quinidine | ↑ antiarrhythmics | Contraindicated due to potential for cardiac arrhythmias <i>[see Contraindications (4]]</i> . |
| Antiarrhythmics: disopyramide, lidocaine, mexiletine | ↑ antiarrhythmics | Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with ritonavir, if available. |
| Anticancer Agents: abemaciclib, apalutamide, | ↑ anticancer agents ↓ ritonavir [#] | Apalutamide is contraindicated due to potential for loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors <i>(see</i> <i>Contraindications (4))</i> . |
| dasatinib, | 1 | Avoid co-administration of encorafenib or ivosidenib with ritonavir due to |

Avoid co-administration of encoratenib or ivosidenib with ritonavir due to potential risk of serious adverse events such as QT interval prolongation. If coadministration of encorafenib with ritonavir cannot be avoided, modify dose as recommended in encorafenib USPI. If coadministration of ivosidenib with wir cannot be avoided, reduce ivosidenib dose to 250 mg once daily

Ritonavir oral solution contains alcohol. You should not take ritonavir oral

| Ritonavir is administr | | should be swallowed whole, and no | ot chewed, broken or crushed. T | ake ritonavir with meals. | There have been reports of increased | | | | | ivosidenib, neratinib, | | ritonavir cannot be avoided, reduce ivosidenib dose to 250 mg once daily. |
|---|---|--|--|--|---|--|--|---|---|--|--|---|
| <u>General Dosing Guidelines</u> Patients who take the 600 I |) mg twice daily soft gel capsu | le ritonavir dose may experience m | ore gastrointestinal side effect | ts such as nausea, vomiting, | treated with protease inhibitors. In so inhibitors was continued or reintroduce | | | | | nilotinib, venetoclax, | | Avoid use of neratinib, venetoclax or ibrutinib with ritonavir For vincristine and vinblastine, consideration should be given to temporarily with |
| | | gel capsule to the tablet formulatio t gel capsule <i>[see Clinical Pharma</i> | | | 5.12 Resistance/Cross-resistance Varying degrees of cross-resistance an | | bitors have been observed. Continue | ed administration of ritona | ir 600 ma twice daily following | vinblastine, vincristine | | holding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when ritonavir is |
| adverse events (gastrointes | stinal or paresthesias) may din | | | | loss of viral suppression may increase t | | | | | vincristine | | administered concurrently with vincristine or vinblastine. |
| 2.3 Dosage Recommen Recommended Dosage for T | | | | | 5.13 Laboratory Tests Ritonavir has been shown to increase | trialycerides, cho | esterol, SGOT (AST), SGPT (ALT) | GGT. CPK. and uric acid | Appropriate Jaboratory testing | | | Clinicians should be aware that if the ritonavir containing regimen is withheld for a prolonged period, consideration should be given to altering the regimen to |
| The recommended dosage of | of ritonavir is 600 mg twice | daily by mouth to be taken with m ppropriate ritonavir plasma levels. | | | should be performed prior to initiating r | | | | | | | not include a CYP3A or P-gp inhibitor in order to control HIV-1 viral load. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and |
| daily and increased at 2 to 3 | 3 day intervals by 100 mg twid | ce daily. The maximum dose of 600 | | | 6 ADVERSE REACTIONS The following adverse reactions are dis | scussed in greater o | detail in other sections of the labelir | ıg. | | | | dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as ritonavir. Please refer to the nilotinib and dasatinib |
| the titration <i>(see Dosage and</i> <u>Pregnant Women</u> | nd Administration (2.6)]. | | | | Drug Interactions <i>(see Warnings</i>) Hepatotoxicity <i>(see Warnings al</i>) | s and Precautions (| (5.1)] | | | | | prescribing information for dosing instructions. |
| | | nancy due to its alcohol content. R | Ritonavir oral solution contains | s the excipients alcohol and | Percentitis / see Warnings and a Pancreatitis / see Warnings and a | | | | | Anticoagulant: warfarin | ↑↓ warfarin | Initial frequent monitoring of the INR during ritonavir and warfarin co- administration is recommended. |
| 1 17 07 | ndations in Pediatric Patien | its | | | Allergic Reactions/Hypersensiti When co-administering ritonavir with | | | nformation for that prote | ase inhihitor including adverse | Anticoagulant: | ↑ rivaroxaban | Avoid concomitant use of rivaroxaban and ritonavir. Co-administration of |
| | | troviral agents <i>[see Dosage and Ad</i> er m ² twice daily by mouth to be tal | | | reactions. | rother protouse in | | | ase minister menduning develop | rivaroxaban Anticonvulsants: carbamazepine, | ↑ anticonvulsants | ritonavir and rivaroxaban may lead to risk of increased bleeding. A dose decrease may be needed for these drugs when co-administered with |
| Ritonavir should be started | d at 250 mg per m² twice daily | and increased at 2 to 3 day interv | als by 50 mg per m² twice daily | y. If patients do not tolerate | 6.1 Clinical Trial Experience Because clinical trials are conducted u | nder widelv varvin | o conditions, adverse reactions rate | es observed in the clinical t | ials of a drug cannot be directly | clonazepam, ethosuximide | | ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available. |
| | | e highest tolerated dose may be u d be considered <i>[see Dosage and Ad</i> | | in combination with other | compared to rates in the clinical trials o | | | | , | Anticonvulsants: divalproex, lamotrigine, | \downarrow anticonvulsants | A dose increase may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these |
| Pediatric Dosage Guidelines Ritonavir oral solution shoul | | nates before a postmenstrual age (i | first day of the mother's last m | nenstrual neriod to birth plus | <u>Adverse Reactions in Adults</u> The safety of ritonavir alone and in con | mbination with oth | er antiretroviral agents was studied | l in 1,755 adult patients. T | able 2 lists treatment-emergent | phenytoin | | anticonvulsants, if available. |
| the time elapsed after birth) | n) of 44 weeks has been attaine | ed [see Warnings and Precautions (5 | 5.2)]. | | Adverse Reactions (with possible or pr combined Phase II/IV studies. | robable relationship | p to study drug) occurring in greater | than or equal to 1% of ad | It patients receiving ritonavir in | Antidepressants: nefazodone, selective serotonin | ↑ antidepressants | A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| | | nd propylene glycol. Special attent g information and dosing instructio | | | The most frequently reported adverse | | | | | reuptake inhibitors (SSRIs): e.g. fluoxetine, paroxetine, | | |
| | | mounts of alcohol and propylene g ount in order to avoid toxicity from | | | gastrointestinal (including diarrhea, na paresthesia), rash, and fatigue/astheni | | abdominal pain (upper and lower)), | neurological disturbances | including paresthesia and oral | tricyclics: e.g. amitriptyline, | | |
| Overdosage (10)]. When pos | ssible, dose should be administ | ered using a calibrated dosing syrin | | | Table 2. Treatment-Emergent Adve equal to 1% of Adult Patients Receiv | | | | Occurring in greater than or | nortriptyline Antidepressant: | ↓ bupropion | Patients receiving ritonavir and bupropion concurrently should be monitored for |
| Table 1. Pediatric Dosage | e Guidelines for Oral Solutio | on* | | | Adverse Reactions | vilig hitoliavir ili | combined Phase n/1v Studies (N | = 1,755) n | % | bupropion | ↓ active metabolite, hydroxybupropion | an adequate clinical response to bupropion. |
| Body Surface Area (m²) | Twice Daily Dose 250 mg per m² | Twice Daily Dose 300 mg per m ² | Twice Daily Dose 350 mg per m ² | Twice Daily Dose 400 mg per m ² | Eye disorders Blurred vision | | | 113 | 6.4 | Antidepressant: | ↑ desipramine | Dosage reduction and concentration monitoring of desipramine is recommended. |
| 0.20 | 0.6 mL (50 mg) | 0.75 mL (60 mg) | 0.9 mL (70 mg) | 1 mL (80 mg) | Gastrointestinal disorders | n - 10 | | | | desipramine Antidepressant: | ↑ trazodone | Adverse events of nausea, dizziness, hypotension and syncope have been |
| 0.25 | 0.8 mL (62.5 mg) 1.6 mL (125 mg) | 0.9 mL (75 mg) 1.9 mL (150 mg) | 1.1 mL (87.5 mg) 2.2 mL (175 mg) | 1.25 mL (100 mg) 2.5 mL (200 mg) | Abdominal Pain (upper and lo Diarrhea including severe wi | | alance* | 464 1,192 | 26.4 67.9 | trazodone | | observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. |
| 0.75 | 2.3 mL (187.5 mg) | 2.8 mL (225 mg) | 3.3 mL (262.5 mg) | 3.75 mL (300 mg) | Dyspepsia | , | | 201 142 | 11.5 8.1 | Antiemetic: | ↑ dronabinol | A dose decrease of dronabinol may be needed when co-administered with |
| 1 1.25 | 3.1 mL (250 mg) 3.9 mL (312.5 mg) | 3.75 mL (300 mg) 4.7 mL (375 mg) | 4.4 mL (350 mg) 5.5 mL (437.5 mg) | 5 mL (400 mg) 6.25 mL (500 mg) | Flatulence Gastrointestinal hemorrhage | 9* | | 41 | 2.3 | dronabinol Antifungals: | ↑ ketoconazole | ritonavir. High doses of ketoconazole or itraconazole (greater than 200 mg per day) are |
| 1.50 | 4.7 mL (375 mg) | 5.6 mL (450 mg) | 6.6 mL (525 mg) | 7.5 mL (600 mg) | Gastroesophageal reflux dise Nausea | ease (GERD) | | 19 1,007 | 1.1 57.4 | ketoconazole itraconazole voriconazole | ↑ itraconazole ↓ voriconazole | not recommended. Co-administration of voriconazole and ritonavir doses of 400 mg every 12 hours |
| | of the oral solution is 80 |) mg per mL. | | | Vomiting* | | | 559 | 31.9 | | 1 Vonconazore | or greater is contraindicated due to the potential for loss of antifungal response |
| Body surface area (BSA) car | | | _ | | General disorders and adminis Fatigue including asthenia* | stration site cond | ditions | 811 | 46.2 | | | [see Contraindications (4)]. Co-administration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/risk to the |
| | I | $BSA (m^2) = \sqrt{\frac{Ht (Cm) \times Wt (kg)}{3600}}$ | _ | | Hepatobiliary disorders | | | | | Anti-neut | A colobicing | patient justifies the use of voriconazole. |
| 2.6 Dose Modification | | 3000 | | | Blood bilirubin increased (incl Hepatitis (including increased | | * | 25 153 | 1.4 8.7 | Anti-gout: colchicine | ↑ colchicine | Contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment <i>[see Contraindications (4]]</i> . |
| | | other protease inhibitors: atazanavi n and clinical study information of t | | | Immune system disorders | | | 114 | 0.2 | | | For patients with normal renal or hepatic function: Treatment of gout flares-co-administration of colchicine in patients on ritonavir: |
| | | <i>5.1</i>), and <i>Drug Interactions (7)</i> . | these procease inhibitors in they | y are co-autimistered with a | Hypersensitivity including urt Metabolism and nutrition disord | | ema^ | 114 | 8.2 | | | 0.6 mg (one tablet) for one dose, followed by 0.3 mg (half tablet) one hour later. |
| 3 DOSAGE FORMS A | | | | | Edema and peripheral edema Gout* | * | | 110 24 | 6.3 1.4 | | | Dose to be repeated no earlier than three days. |
| Ritonavir Tablets US White to off white, capsule s | | ebossed with 'H' on one side and 'R9 | 9' on other side. | | Hypercholesterolemia* | | | 52 | 3 | | | Prophylaxis of gout flares-co-administration of colchicine in patients on ritonavir: If the original colchicine regimen was 0.6 mg twice a day, the regimen should be |
| 4 CONTRAINDICATI | | Annual Schühlteren und Alter Kulturen | | | Hypertriglyceridemia* Lipodystrophy acquired* | | | 158 51 | 9 2.9 | | | adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6 mg |
| when co-administer contraindication info | | tease inhibitors, see the full pres | scribing information for that j | protease inhibitor including | Musculoskeletal and connective | e tissue disorders | S | | | | | once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine |
| Ritonavir is contrain ritonavir or any of its | | wn hypersensitivity (e.g., toxic epic | dermal necrolysis (TEN) or Ste | evens-Johnson syndrome) to | Arthralgia and back pain Myopathy/creatine phosphok | * kinase increased* | | 326 66 | 18.6 3.8 | | | in patients on ritonavir: |
| Ritonavir is contrain | ndicated with drugs that are h | highly dependent on CYP3A for cle | | | Myalgia Norveyo ovetem disordore | | | 156 | 8.9 | Anti-infective: | ↑ clarithromycin | Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). For patients with renal impairment, adjust clarithromycin dose as follows: |
| | rious and/or life-threatening rea renoreceptor Antagonist : alfuz | actions <i>[see Drug Interactions (7.1)</i> | and Clinical Pharmacology (12. | .3//. | Nervous system disorders | | | | | | oran only on | |
| Alpha 1 - Adre | renoreceptor Antayonist : anuz | zosin | | | Dizziness* | | | 274 | 15.6 | clarithromycin | | For patients with CL_{CR} 30 to 60 mL per min the dose of clarithromycin should be advect by 50% |
| Antianginal: r | : ranolazine | | 10 | | Dysgeusia* | aresthesia)* | | 285 | 16.2 | clarithromycin | | For patients with CL_{ck} 30 to 60 mL per min the dose of clarithromycin should be reduced by 50%. For patients with CL_{ck} less than 30 mL per min the dose of clarithromycin |
| Antianginal: r Antiarrhythm Antifungal: v | : ranolazine mics: amiodarone, dronedaron voriconazole | zosın e, flecainide, propafenone, quinidin | 10 | | | aresthesia)* | | | | clarithromycin | | should be reduced by 50%. For patients with CL_{cn} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. |
| Antianginal: r Antiarrhythm Antifungal: v Anti-gout: co | : ranolazine mics: amiodarone, dronedaron voriconazole | | 10 | | Dysgeusia* Paresthesia (including oral pa Peripheral neuropathy Syncope* | aresthesia)* | | 285 889 | 16.2 50.7 | Antimycobacterial: | ↑ bedaquiline | should be reduced by 50%. For patients with CL _{ex} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with hormal renal function is necessary. Bedaquiline should only be used with ritonavir if the benefit of co-administration |
| Antianginal: a Antiarrhythm Antifungal: v Anti-gout: co Anti-gout: co Ergot Derivat | : ranolazine mics: amiodarone, dronedaron voriconazole olchicine tics: lurasidone, pimozide atives: dihydroergotamine, ergu | e, flecainide, propafenone, quinidin | 10 | | Dysgeusia* Paresthesia (including oral pa Peripheral neuropathy | aresthesia)* | | 285 889 178 58 52 | 16.2 50.7 10.1 3.3 3 | | ↑ bedaquiline ↑ rifabutin and | should be reduced by 50%. For patients with Ct_{ca} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary. |
| Antianginal: 1 Antiarrhythm Anti-gout: co Anti-gout: co Anti-gout: co Anti-gout: co Gi MotilityA HMG-CoA Re | : ranolazine mics: amiodarone, dronedaron voriconazole olchicine tics: lurasidone, pimozide atives: dihydroergotamine, ergi gent: cisapride leductase Inhibitors: lovastatir | e, flecainide, propafenone, quinidin otamine, methylergonovine 1, simvastatin | 18 | | Dysgeusia* Paresthesia (including oral pa Peripheral neuropathy Syncope* Psychiatric disorders Confusion* Disturbance in attention | aresthesia)* | | 285 889 178 58 | 16.2 50.7 10.1 3.3 | Antimycobacterial: bedaquiline | · · | should be reduced by 50%. For patients with CL _{cs} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary. Bedaquiline should only be used with ritonavir if the benefit of co-administration outweights the risk. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg per day is recommended (e.g., 150 mg every other day or three times |
| Antianginal: n Antiarrhythm Antifungal: v Anti-gout: co Antipsychoti Ergot Derivat GI Motility A; HMG-CoA Re Microsumat | : ranolazine mics: amiodarone, dronedaron voriconazole olchicine dicki lurasidone, pimozide atives: dihydroergotamine, ergu Agent: cisapride eductase Inhibitors: lovastatir i triglyceride transfer protein (N | e, flecainide, propafenone, quinidin otamine, methylergonovine 1, simvastatin ATTP) Inhibitor: Iomitapide | | | Dysgeusia* Paresthesia (including oral pa Peripheral neuropathy Syncopa* Psychiatric disorders Confusion* Disturbance in attention Renal and urinary disorders Increased urination* | | | 285 889 178 58 52 | 16.2 50.7 10.1 3.3 3 | Antimycobacterial: bedaquiline Antimycobacterial: rifabutin Antimycobacterial: | ↑ rifabutin and | should be reduced by 50%. For patients with CL _{x3} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary. Bedaquiline should only be used with ritonavir if the benefit of co-administration outweighs the risk. Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg per day is recommended (e.g., 150 mg every other day or three times a week). Further dosage reduction may be necessary. May lead to loss of virologic response. Alternate antimycobacterial agents such |
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Kitudy 247 Advanced Patier Ritonavir Pla | 16.2 50.7 10.1 3.3 3 2.5 4.2 21.7 15.9 3.8 12.2 27.1 13.2 3.3 1.7 1.2 Abnormalities Occurring in ts PI-Naive Patients Saquinavir | Antimycobacterial: bedaquiline Antimycobacterial: rifabutin Antimycobacterial: rifampin Antiparasitic: atovaquone Antiparasitic: quinine Antipsychotics: lurasidone pimozide Antipsychotics: gerbenazine, risperidone, thioridazine Antipsychotics: quetiapine β-Blockers: metoprolol, timolol Bronchodilator: theophylline | ↑ rifabutin and rifabutin metabolite ↓ ritonavir ↓ atovaquone ↑ quinine ↑ lurasidone ↑ pimozide ↑ antipsychotics ↑ quetiapine ↑ beta-blockers ↓ theophylline | should be reduced by 50%. For patients with CL_{ca} less than 30 mL per min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary. Bedaquiline should only be used with ritonavir if the benefit of co-administration outweighs the risk. 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These inte ly leading to severe, life-threatenin er exposures of ritonavir . a development of resistance. hibitors, see the full prescribing in sible and known significant drug in tions prior to and during ritonavir i d with the concomitant medications l and propylene glycol. When adr , which may lead to elevated conce nished ability to metabolize propyli f cardiac toxicity (including comp tates in the immediate postnatal pe ants intemendiate postnatal and propylene glycol. When adr , which may lead to elevated conce nished ability to metabolize propyli of cardiac toxicity related to ritonavir and for toxicity related to ritonavir of form all medicines that are to be <i>inistration</i> (2.4) and Overdosage (10 upper limit of normal, clinical he l drugs (see Table 3). There may be | ry arterial hypertension nificantly reduced ritonavir pla- nd cross-resistance/ <i>see Drug In</i> YP3A or initiation of medicatio tabolized by CYP3A. Initiation of aractions may lead to: ng, or fatal events from greate nformation for that protease in nteractions, including dosing r therapy; review concomitant r <i>s (see Contraindications (4)</i> and ministered concomitantly with anttations. Preterm neonates m ene glycol, thereby leading to plete AV block, bradycardia, a th have been reported, predom ylene glycol. ariod because of possible toxici ighs the potential risks, infants r oral solution including: hyper es, hypotonia, cardiac arrhythe e given to infants should be tai <i>0//.</i> | nteractions (7.2) and Clinical Ins metabolized by CYP3A in of medications that inhibit or or exposures of concomitant nhibitor including important recommendations <i>(see Drug</i> medications during ritonavir I Drug Interactions (77). h propylene glycol, alcohol nay be at an increased risk of accumulation and potential and cardiomyopathy), lactic inantly in preterm neonates tites. However, if the benefit is should be monitored closely rosmolality, with or without mias and ECG changes, and ken into account in order to curred in patients receiving ninase elevations in patients | Dysgeusia* Paresthesia (including oral pa Peripheral neuropathy Syncopa* Psychiatrie disorders Confusion* Disturbance in attention Renal and urinary disorders Increased urination* Respiratory, thoracic and media Coughing* Oropharyngeal Pain* Skin and subcutaneous tissue d Acne* Pruritus* Rash (includes erythematous Vascular disorders Flushing, feeling hot* Hypertension* Hypertension* Table 3 shows the percentage of Adult Pati greater than 3% of Patients Receivi CPripheral coldness* * Represents a medical concept includence of Adult Pati greater than 3% of Patients Receivi Cholesterol > 240 mg/dL CPR > 1000 IU/L GGT > 300 IU/L SGT (AST) > 180 | astinal disorders iisorders iisorders iand maculopapula istatic hypotension* cluding several simi patients who deve ents, by Study a ing Ritonavir plus ZDV Ritonavir 9.6 1.8 5.3 5.3 5.3 9.6 1.8 | Iteration and the second second | 285 889 178 58 52 44 74 380 279 67 214 475 232 58 30 21 ties. mistry and Hematology Study 247 Advanced Patier 36.5 9.1 19.6 19.6 12.6 12.6 12.6 17.3 | 16.2 50.7 10.1 3.3 3 2.5 4.2 21.7 15.9 3.8 12.2 27.1 13.2 3.3 1.7 13.2 3.3 1.7 13.2 3.3 1.7 1.2 23.3 9.9 1.3 9.9 1.3 9.9 1.3 9.9 1.3 9.2 7 7.8 .4 23.4 .4 3.3 | Antimycobacterial: bedaquiline Antimycobacterial: rifabutin Antiparasitic: atovaquone Antiparasitic: quinine Antipsychotics: lurasidone pimozide Antipsychotics: perphenazine, risperidone, thioridazine Antipsychotics: quetiapine Antipsychotics: quetiapine Biockers: metoprolol, timolol Bronchodilator: theophylline Calcium channel blockers: diltiazem, nifedipine, verapamil Digoxin Endothelin receptor antagonists: bosentan | <pre>↑ rifabutin and rifabutin metabolite ↓ ritonavir ↓ atovaquone ↑ quinine ↑ lurasidone ↑ pimozide ↑ antipsychotics ↑ quetiapine ↑ beta-blockers ↓ theophylline ↑ calcium channel blockers ↑ digoxin</pre> | should be reduced by 50%. 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Postmarka acidosis, renal toxicit from these exits. 5.3 Hepatotoxicity Hepatot cra | : ranolazine mics: amiodarone, dronedaron voriconazole ochicine tics: lurasidone, pimozide atives: dihydroergotamine, ergr Agent: cisapride leductase Inhibitors: lovastatin triglyceride transfer protein (Ik tor: sildenafii (Revatio®) when ynorics: triazolam, orally admi ndicated with drugs that are p potential for loss of virologi or 3//. Agents: apalutamide ucts: St. John's Wort (hypericu PRECAUTIONS Iverse Reactions Due to Dru P32 Inhibitor, in patients recei ritonavir, may increase plasma e or decrease concentrations o t adverse reactions, potentiall tadverse reactions associated m Neonates interabelism of propylene glycol de adverse events due to dimi reting life-threatening cases o re, CNS depression and respirar or al solution which also cont uld not be used in preterm neori ion to treat HIV infection in infe nolality and serum creatinine, ity, CNS depression (including of ethanol and propylene glyc, xcipients /see Dosage and Admi vations exceeding 5 times the nation with other antiretroviras or C. Therefore, caution shou repartitis. 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solution during pregnancy because there is no known safe level of alcohol exposure during pregnancy. Tell your healthcare provider if you become pregnant during treatment with ritonavir.

- Ritonavir may reduce how well hormonal birth control works. Females who 0 may become pregnant should use another effective form of birth control or an additional barrier method of birth control during treatment with ritonavir.
- Pregnancy Registry: There is a pregnancy registry for women who take 0 antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take ritonavir. • You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
- Ritonavir may pass into your breastmilk.

• are pregnant or plan to become pregnant.

Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with ritonavir. Keep a list of your medicines to show our healthcare provider and pharmacist.

- · You can ask your healthcare provider or pharmacist for a list of medicines that interact with ritonavir.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take ritonavir with other medicines.

How should I take ritonavir?

- Take ritonavir exactly as your healthcare provider tells you to take it.
- You should stay under a healthcare provider's care during treatment with ritonavir. Do not change your dose of ritonavir or stop your treatment without talking with your healthcare provider first.
- If your child is taking ritonavir, your child's healthcare provider will decide the right dose based on your child's height and weight. Tell your healthcare provider if your child's weight changes. If your child does not tolerate ritonavir oral solution, ask your child's healthcare provider for advice.
- Swallow ritonavir tablets whole. Do not chew, break, or crush tablets before swallowing. If you cannot swallow ritonavir tablets whole, tell your healthcare provider. You may need a different medicine.
- Take ritonavir with meals.
- Do not run out of ritonavir. Get your ritonavir prescription refilled from your healthcare provider or pharmacy before you run out.
- If you miss a dose of ritonavir, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, wait and take the next dose at the regular time. Do not double the next dose.
- If you take too much ritonavir, call your local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of ritonavir?

- Ritonavir can cause serious side effects including:
- · See "What is the most important information I should know about ritonavir?"
- Liver problems. Some people taking ritonavir in combination with other antiviral medicines have developed liver problems which may be life-threatening. Your healthcare provider should do regular blood tests during your combination treatment with ritonavir. If you have chronic hepatitis B or C infection, your healthcare provider should check your blood tests more often because you have an increased chance of developing liver problems. Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems:
- loss of appetite • yellowing of your skin or whites of your eyes
- pain or tenderness on your
 itchy skin right side below your ribs
- Inflammation of your pancreas (pancreatitis). Ritonavir can cause serious pancreas problems, which may lead to death. Tell your healthcare provider right away if you have signs or symptoms of pancreatitis such as:
- o nausea vomiting
- stomach (abdomen) pain
- Allergic reactions. Sometimes these allergic reactions can become severe and require treatment in a hospital. Call your healthcare provider right away if you develop a rash. Stop taking ritonavir and get medical help right away if you have any of the following symptoms of a severe allergic reaction:
- trouble breathing \circ sweating
- swelling of your face, lips or tongue wheezing
- dizziness or fainting • muscle or joint pain
- throat tightness or hoarseness blisters or skin lesions
- fast heartbeat or pounding in • mouth sores or ulcers your chest (tachycardia)
- Changes in the electrical activity of your heart called PR prolongation. PR

5.3 Hep

5.4 Pan

5.5 Allergic Reactions/Hype

s occurred in greater than 3% of pediatric patients who received treatment with ritonavir either glecaprevir/pibrentasvir The following Grade 3 to 4 laboratory abnorn

Allergic rea ding urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Cases of anaphylaxis, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome have also been reported. Discontinue treatment if severe reactions develop.

5.6 PR Interval Prolongation Ritonavir prolongs the PR interval in some patients. Post marketing cases of second or third degree atrioventricular block have been reported in patients.

Ritonavir should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease, cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, beta-The impact on the FA interval to co-animastration of interval with other augs that proving the FA interval including calculation channel blockers, beat-adrenergic blockers, digoxin and atzanavity has not been evaluated. As a result, co-administration of ritonavir with these drugs should be undertaken with caution, particularly with those drugs metabolized by CYP3A. Clinical monitoring is recommended [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

5.7 Lipid Disorders

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides (see Advector Reactions (6.1)). 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, taking into account any potential drug-drug interactions with ritonavir and HMG CoA reductase inhibitors /see Contraindications (4) and Drug Interactions (7)).

5.8 Diabetes Mellitus/Hyperglycemia New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance The mode characteristic interaction of the extension of t 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. Consider monitoring for hyperglycemia, new onset diabetes mellitus, or an exacerbation of diabetes mellitus in patients treated with ritonavir.

| alone or in combination with | n reverse transcriptase inhibit | ors: neutropenia (| 9%), | hyperamyla | semia (| 7%), | thrombocytopenia (5%), anemia (4%), and | |
|------------------------------|---------------------------------|--------------------|------|------------|---------|------|---|--|
| elevated AST (3%). | | | | | | | | |

6.2 Postmarketing Experience

The following adverse events (not previously mentioned in the labeling) have been reported during post-marketing use of ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to ritonavir exposure

Body as a Whole

Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope, or renal insufficiency has been reported. Syncope, orthostatic hypotension, and renal insufficiency have also been reported without known dehydration.

Co-administration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.

Cardiovascular System

First-degree AV block, second-degree AV block, third-degree AV block, right bundle branch block have been reported/see Warnings and Precautions (5.6)]

| Cardiac and neurologic events have been reported when ritonavir has been co-administered with disopyramide, mexiletine, nefazodone, fluoxetine, and beta blockers. The possibility of drug interaction cannot be excluded. |
|---|
| Endocrine System |
| Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with fluticasone propionate or budesonide. |
| Nervous System |
| There have been postmarketing reports of seizure. Also, see Cardiovascular System. |

Renal and Urinary Disorders

| simeprevir | ↑ simeprevir | |
|--|----------------------------------|--|
| Herbal Products: St. John's Wort (hypericum perforatum) | ↓ ritonavir | Contraindicated due to potential for loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors <i>[see Contraindications (4]]</i> . |
| Lipid-modifying agents HMG-CoA Reductase Inhibitor: | | |
| lovastatin simvastatin | ↑ lovastatin ↑ simvastatin | Contraindicated due to potential for myopathy including rhabdomyolysis <i>[see Contraindications (4)]</i> . |
| atorvastatin rosuvastatin | ↑ atorvastatin ↑ rosuvastatin | Titrate atorvastatin and rosuvastatin dose carefully and use the lowest necessary dose. If ritonavir is used with another protease inhibitor, see the complete prescribing information for the concomitant protease inhibitor for details on coadministration with atorvastatin and rosuvastatin. |
| Microsomal triglyceride transfer protein | ↑ lomitapide | Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. |
| (MTTP) Inhibitor: | | Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity <i>(see Contraindications (4))</i> . |

prolongation can cause irregular heartbeats. Tell your healthcare provider righ away if you have symptoms such as:

 dizziness • feel faint or pass out

 abnormal heart beat • lightheadedness

Increase in cholesterol and triglyceride levels. Treatment with ritonavir may increase your blood levels of cholesterol and triglycerides. Your healthcare provider should do blood tests before you start your treatment with ritonavir and regularly to check for an increase in your cholesterol and triglycerides levels.

Diabetes and high blood sugar (hyperglycemia). Some people who take protease inhibitors including ritonavir can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often during treatment with ritonavir.

Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get

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stronger and begin to fight infections that have been hidden in your body for a long time. Call your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.

- Change in body fat can happen in some people who taking HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- · Increased bleeding for hemophiliacs. Some people with hemophilia have increased bleeding with protease inhibitors including ritonavir.
- Kidney stones

The most common side effects of ritonavir include:

| • diarrhea | tingling feeling or numbness in hands or feet or around the lips |
|------------------------------|--|
| nausea | • rash |
| vomiting | feeling weak or tired |

 vomiting • upper and lower stomach (abdominal) pain

Ritonavir oral solution contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of ritonavir, it could make

him/her sick from too much alcohol. Go to the nearest emergency room right away if this happens These are not all of the possible side effects of ritonavir. Call your doctor for medical

advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ritonavir tablets?

- Store ritonavir tablets in the original container given to you by the pharmacist.
- Use ritonavir tablets by the expiration date.

Store ritonavir tablets:

- Store below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days permitted.
- Exposure to high humidity outside the original container for longer than 2 weeks is not recommended

Keep ritonavir and all medicines out of the reach of children.

General information about the safe and effective use of ritonavir

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use ritonavir for a condition for which it was not prescribed. Do not give ritonavir to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ritonavir that is written for healthcare professionals.

What are the ingredients in ritonavir tablets?

Active ingredient: ritonavir USP

Inactive ingredients: colloidal silicon dioxide, copovidone, dibasic calcium phosphate anhydrous, sodium stearyl fumarate and sorbitan monolaurate. The tablets are coated with Opadry White which contains colloidal anhydrous silica, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.



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| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comment | <u>Special Populations</u> <i>Gender, Race and Age</i> No age-related pharma older patients. |
|--|---|--|--|
| Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin) | ↑ immunosuppressants | Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir. | A study of ritonavir ph Pharmacokinetic diffe <i>Pediatric Patients</i> |
| Kinase Inhibitors: fostamatinib <i>(also see anticancer agents above)</i> | ↑ fostamatinib metabolite R406 | Monitor for toxicities of R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Fostamatinib dose reduction may be required. | Steady-state pharmac to 400 mg per m ² twic daily in PACTG Study patients than in adult |
| Long-acting beta-adrenoceptor agonist: salmeterol | ↑ salmeterol | Concurrent administration of salmeterol and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. | were comparable to t regarding ritonavir con exposures were not e somewhat lower than |
| Oral Contraceptives or Patch Contraceptives: ethinyl estradiol | ↓ ethinyl estradiol | Alternate methods of contraception should be considered. | concentrations obtain lower, respectively, th <i>Renal Impairment</i> |
| PDES Inhibitors: avanafil sildenafil, tadalafil, vardenafil | ↑ avanafil ↑ sidenafil ↑ tadalafil ↑ vardenafil | Sildenafil when used for the treatment of pulmonary arterial hypertension (Revatio-) is contraindicated due to the potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope (<i>see Contraindications (4I</i>). Do not use ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established. Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil in patients receiving ritonavir. Coadministration of ritonavir with these drugs may result in an increase in PDE5 inhibitor associated adverse events, including hypotension, syncope, visual changes, and prolonged erection. Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH): Sildenafil (Revatio ⁻) is contraindicated <i>(see Contraindications (4I</i>). The following dose adjustments are recommended for use of tadalafil (Adcirca ⁻) with ritonavir: Co-administration of ADCIRCA in patients on ritonavir: In patients receiving ritonavir for at least on eveek, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of ritonavir in patients on ADCIRCA: At 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of ritonavir. At 20 mg once daily. Increase to 40 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for the treatment of erectile dysfunction: It is recommended not to exceed the following doses: • Sildenafi: 25 mg every 48 hours • Vardenafi: 25 mg every 72 hours | Ritonavir pharmacokin body clearance is not e Hapatic Impairment Dose-normalized steat control subjects dosed mg twice-daily, n = 6) ritonavir was not stati with mild or moderat patients with moderat hapatic impairment. Pregnancy Based on evaluation of Drug Interactions Isee also Contraindica. Table 6 and Table 7 su drugs. For information Table 6. Drug Interard Drug Clarithromycin Didanosine Fluconazole Fluoxetine |
| Sedative/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, | ↑ sedative/hypnotics | Use with increased monitoring for adverse events. A dose decrease may be needed for these drugs when co-administered with ritonavir. | Ketoconazole Rifampin |
| zolpidem Sedative/Hypnotics: triazolam, | ↑ triazolam ↑ midazolam | Contraindicated due to potential for prolonged or increased sedation or respiratory depression <i>[see Contraindications (4]]</i> . | Voriconazole |
| orally administered Sedative/Hypnotics: | ↑ triazolam | Contraindicated due to potential for prolonged or increased sedation or | Zidovudine |
| triazolam, orally administered midazolam | ↑ midazolam | respiratory depression <i>[see Contraindications (4]</i>]. | ND = not determined Table 7. Drug Interac |
| Sedative/hypnotics: Parenteral midazolam | ↑ midazolam | Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. | Co-administered Drug Alprazolam Avanafil |
| Stimulant: methamphetamine | \uparrow methamphetamine | Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir. | Clarithromycin |
| Systemic/Inhaled/ Nasal/Ophthalmic Corticosteroids: e.g., betamethasone budesonide | ↑ glucocorticoids | Coadministration with corticosteroids whose exposures are significantly increased by strong CVP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CVP3A inhibitors relative to other studied steroids) should be considered. | 14-OH clarithromycin metabolite Desipramine |
| ciclesonide dexamethasone fluticasone methylprednisolone | | strong of F3A minutors relative to other studied sterousy should be considered, particularly for long-term use. | 2-OH desipramine metabolite |
| mometasone prednisone | | | Didanosine |
| triamcinolone refers to interaction with apalu | utamide. | | Ethinyl estradiol |
| important information for use in spe | th other protease inhibitors | , see the full prescribing information for the co-administered protease inhibitor includin | Fluticasone propionate aqueous nasal spray |
| | | cy outcomes in women exposed to ritonavir during pregnancy. Healthcare providers ar gnancy Registry (APR) at 1–800–258–4263. | Indinavir ¹ Day 14 Day 15 |

Concomitant Drug Class: Effect on Clinical Comment

Special Populations . Race and Age etic differences have been observed in adult patients (18 to 63 years). Ritonavir pharmacokinetics have not been studied in -related pharmacok

atients. y of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir.

acokinetic differences due to race have not been identified. ric Patients

state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg per m² twice-daily mg per m² twice-daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg per m² twice-PACTO Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m²) was approximately 1.5 to 1.7 times faster in pediatric ts than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg per m² twice daily in pediatric patients greater than 2 years omparable to those obtained in adults receiving 600 mg (approximately 330 mg per m²) twice-daily. The following observations were seen ng ritonavir concentrations after administration with 350 or 450 mg per m² twice-daily in children less than 2 years of age. Higher ritonavir res were not evident with 450 mg per m² twice-daily compared to the 350 mg per m² twice-daily. Ritonavir trough concentrations were rhat lower than those obtained in adults receiving 600 mg twice-daily. The area under the ritonavir plasma concentration time curve and trough rations obtained after administration with 350 or 450 mg per m² twice-daily in children less than 2 years were approximately 16% and 60% respectively, than that obtained in adults receiving 600 mg twice daily

. vir pharmacokinetics have not been studied in patients with renal impairment, however, since renal clearance is negligible, a decrease in total earance is not expected in patients with renal impairmen

c Impairment

malized steady-state ritonavir concentrations in subjects with mild hepatic impairment (400 mg twice-daily, n = 6) were similar to those in subjects dosed with 500 mg twice-daily. Dose-normalized steady-state ritonavir exposures in subjects with moderate he tic impairment (400 ice-daily, n = 6) were about 40% lower than those in subjects with normal benatic function (500 mg twice-daily, n = 6). Protein binding of was not statistically significantly affected by mild or moderately impaired hepatic function. No dose adjustment is recommended in patients nild or moderate hepatic impairment. However, health care providers should be aware of the potential for lower ritonavir concentrations in with moderate hepatic impairment and should monitor patient response carefully. Ritonavir has not been studied in patients with severe c impairment

etoconazole

on evaluation of the published literature, ritonavir exposures are reduced during pregnancy relative to postpartum

nteractions o Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]

5 and Table 7 summarize the effects on AUC and C 🛶, with 95% confidence intervals (95% CI), of co-administration of ritonavir with a variety of For information about clinical recommendations see Table 4 in *Drug Interactions (7)*.

. Drug Interactions - Pharmacokinetic Parameters for Ritonavir in the Presence of the Co-administered Drug

| Co-administered Drug | Dose of Co-administered Drug (mg) | Dose of Ritonavir (| mg) | N | AUC % (95% CI) | C _{max} (95% CI) | C _{min} (95% CI) |
|---|---|-----------------------------|-----------------|--------------------------|--------------------|------------------------------|------------------------------------|
| Clarithromycin | 500 q12h, 4 d | 200 q8h, 4 d | | 22 | ↑ 12% (2, 23%) | ↑ 15% (2, 28%) | ↑ 14% (-3, 36%) |
| Didanosine | 200 q12h, 4 d | 600 q12h, 4 d | | 12 | \leftrightarrow | \leftrightarrow | \leftrightarrow |
| Fluconazole | 400 single dose, day 1; 200 daily, 4 d | 200 q6h, 4 d | | 8 | ↑ 12% (5, 20%) | ↑ 15% (7, 22%) | ↑ 14% (0, 26%) |
| Fluoxetine | 30 q12h, 8 d | 600 single dose, 1 | d | 16 | ↑ 19% (7, 34%) | \leftrightarrow | ND |
| Ketoconazole | 200 daily, 7 d | 500 q12h, 10 d | | 12 | ↑ 18% (-3, 52%) | ↑ 10% (-11, 36%) | ND |
| Rifampin | Rifampin 600 or 300 daily, 10 d | | | 7, 9* | ↓ 35% (7, 55%) | ↓ 25% (-5, 46%) | ↓ 49% (-14, 91%) |
| Voriconazole | 400 q12h, 1 d; then 200 q12h, 8 d | 400 q12h, 9 d | | | \leftrightarrow | \leftrightarrow | ND |
| Zidovudine | 200 q8h, 4 d | 300 q6h, 4 d | | 10 | \leftrightarrow | \leftrightarrow | \leftrightarrow |
| ND = not determine | ed | | | | | • | |
| able 7. Drug Inter | actions - Pharmacokinetic Pa | arameters for Co-admi | nistere | d Drug in t | he Presence of | Ritonavir | |
| Co-administered Drug | Dose of Co- administered Drug (mg | Dose of) Ritonavir (mg) | N | | UC % i% CI) | C _{max} (95% CI) | C _{min} (95% CI) |
| Alprazolam | 1, single dose | 500 q12h, 10 d | 12 | ↓129 | % (-5, 30%) | ↓ 16 %(5, 27%) | ND |
| Avanafil | 50, single dose | 600 q12h | 14 ⁶ | ↑ 13·f | fold | ↑ 2.4-fold | ND |
| Clarithromycin 14-OH clarithromycin metabolite | 500 q12h, 4 d | 200 q8h, 4 d 22 | | ↑ 77% (56, 1 ↓ 100 | 03%) | ↑ 31% (15, 51%) ↓ 99% | ↑ 2.8-fold (2.4 3.3X) ↓ 100% |
| Desipramine | 100, single dose | 500 q12h, 12 d | 14 | | 45% 211%) % | ↑ 22% (12, 35%) | ND ND |

| | | 14 | ↑ 145% (103, 211%) ↓ 15% (3, 26 %) | (12, 35%) ↓ 67% (62, 72%) | ND | Manufactured for: Camber Pharmaceu Piscataway, NJ 08 |
|--------------------|------------------|----|---|---------------------------------|-------------------------|--|
| 200 q12h, 4 d | 600 q12h, 4 d | 12 | ↓ 13% (0, 23%) | ↓ 16% (5, 26%) | \leftrightarrow | |
| 50 mcg single dose | 500 q12h, 16 d | 23 | ↓ 40% (31, 49%) | ↓ 32% (24, 39%) | ND | Hetero Labs Limited Jeedimetla, Hyderabad - 500 09 |
| 200 mcg qd, 7 d | 100 mg q12h, 7 d | 18 | ↑ approximately 350-fold⁵ | ↑ approximately 25·fold⁵ | | India Revised: 02/2023 |
| 400 q12h, 15 d | 400 q12h, 15 d | 10 | ↑ 6% (-14, 29%) | ↓ 51% (40, 61%) | ↑ 4-fold (2.8, 6.8X) | |

⊥7%

4.3X)

12

(-22, 28%)

↑ 3.4-fold (2.8,

equivalent tight container (60 mL or less). For patient use: exposure of this product to high humidity outside the original or USP equivalent tight container (60 mL or less) for longer than 2 weeks is not 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

General Administration Information/see Dosage and Administration (2)]:

- Advise patients and caregivers to pay special attention to accurate preparation and administration of their dose to minimize the risk of accidental overdose or underdose of ritonavir.
- Advise caregivers to inform their healthcare provider if their child's weight changes in order to make sure that the child's ritonavir dose is adjusted as needed.

Advise patients to take ritonavir with meals.

- For adult patients taking ritonavir tablets, the maximum dose of 600 mg twice daily by mouth with meals should not be exceeded. Advise patients to remain under the care of a physician while using ritonavir and to take ritonavir and other concomitant antiretroviral therapy every day as prescribed. Ritonavir must always be used in combination with other antiretroviral drugs. Advise patients not to alter the dose or ntinue therapy without consulting with their healthcare provider. If a dose of ritonavir is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.
- Continued ritonavir therapy at a dose of 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-res
- other protease inhibitors Ritonavir is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including stic infections. Patients should remain under the care of a physician when
- <u>Drug Interactions</u>
 Ritonavir may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non
- prescription medication or herbal products, particularly St. John's Wort.
- Instruct patients receiving combined hormonal contraception to use an effective alternative contraceptive method or an additional barrier method during therapy with ritonavir because hormonal levels may decrease *[see Drug Interactions (7.2), Use in Specific Populations (8.3)]*. <u>epatotoxicity</u>

Pre-existing liver disease including Hepatitis B or C can worsen with use of ritonavir. This can be seen as worsening of transaminase elevations or The existing their based including reporting to the an worse in trace of monotor. This can be seen as worsening the international second processing the se loss of appetite, abdominal pain, jaundice, and itchy skin /see Warnings and Precautions (5.3).

Pancreatitis Pancreatitis, including some fatalities, has been observed in patients receiving ritonavir therapy. Advise patients to notify their healthcare provider of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis / see Warnings and Precautions (5.4)/.

Allergic Reactions/Hypersensitivity Skin rashes ranging in severity from mild to Stevens-Johnson syndrome have been reported in patients receiving ritonavir. Advise patients to contact

their healthcare provider if they develop a rash while taking ritonavir [see Warnings and Precautions (5.5]]. PR Interval Prolongation

changes in the electrocardiogram (e.g., PR prolongation). Advise patients to consult their healthcare provider if they experience

symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness [see Warnings and Precautions (5.6]]. Lipid Disorders

Advise patients that treatment with ritonavir therapy can result in substantial increases in the concentration of total cholesterol and triglycerides [see Warnings and Precautions (5.7)].

Diabetes Mellitus/Hyperglycemia

Advise patients that new onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported and to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or nusual weight loss and/or an increased blood sugar while on ritonavir as they may require a change in their diabetes treatment or new treatm Warnings and Precautions (5.8)].

Immune Reconstitution Syndrome

Advise patients that immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy including ritonavir [see Warnings and Precautions (5.9)]. Fat Redistribution

Advise patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time [see Warnings and Precautions (5. 10]].

Patients with Hemophilia Advise patients with hemophilia that they may experience increased bleeding when treated with protease inhibitors such as ritonavir (see Warnings and Precautions (5.11)].

Ritonavir Oral Solution Not Recommended During Pregnancy

Advise pregnant women that use of ritonavir oral solution during pregnancy is not recommended due to its alcohol content (see Dosage and Administration (2.3) and Use in Specific Population (8.1)].

Pregnancy Exposure Registry rm patients that there is an antiretroviral pregnancy registry that monitors fetal outcomes of pregnant women exposed to ritonavir /see Use in

Specific Populations (8.1)].

Lactation nstruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk */see Use in Specific Populations (8.2)*

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↑ 4-fold

(2.5, 6.5X)

ND

↓ 62%

↑ 55%

40. 72%)

(52, 70%)

By: HETERO[™] Hetero Labs Limited Jeedimetla, Hyderabad - 500 055, India

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Revised: 02/2023

and rabbits. During organogenesis in the rat and rabbit, systemic exposure (AUC) was approximately 1/3 lower than human exposure at the recommended daily dose. In the rat pre- and post-natal developmental study, maternal systemic exposure to ritonavir was approximately 1/2 of the exposure in humans at the recommended daily dose, based on a body surface area conversion factor *[see Data]*. Ritonavir oral solution is not recommended during pregnancy because there is no known safe level of alcohol exposure during pregnancy [see Clinical

birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) /see Datal.

Considerations, Dosage and Administration (2.3) and Warnings and Precautions (5.2)]. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population is because population is a background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are not sufficient to adequately assess the risk of birth defects or miscarriage. Available data from the APR show no difference in the rate of overall birth defects for ritonavir compared to the background rate for major

tudies, no evidence of adverse developmental outcomes was observed with oral administration of ritonavir

Clinical Considerations Dose Adjustments During Pregnancy and the Postpartum Period

Risk Summary

Ritonavir oral solution contains alcohol and proylene glycol and is not recommended during pregnancy because there is no known safe level of alcohol exposure during pregnancy *[see Dosage and Administration (2.3)* and *Warnings and Precautions (5.2)]*.

Human Data Based on prospective reports to the APR of approximately 6100 live births following exposure to ritonavir-containing regimens (including over 2800 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The lence of birth defects in live births was 2.3% (95% Cl: 1.7% to 2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.3% to 3.5%) following second and third trimester exposure to ritonavir-containing regimens.

While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair. Animal Data Bitonavir was administered or ally to pregnant rats (at 0, 15, 35, and 75 molko/day) and rabbits (at 0, 25, 50, and 110 molko/day) during organogenesi

In toriant was administered on any oppregnant ratis (at.), 15, 35, and 25 migragidary and radio is (at.), 25, 05, and 15 migragidary and an oppression (a section days 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at doses producing systemic exposures (AUC) equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. Developmental taxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dose, at an exposure equivalent to approximately 1/3 lower than human exposure at the recommended daily dose. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 1/5 lower than human exposure at the recommended daily dose, beelopmental toxicity was beerved in rabits (resorptions, decreased litter size and decreased fetal weights) at maternally toxic doses approximately 1.8 times higher than the recommended daily dose, based on a body surface area conversion factor. In pre-and postnatal development study in rats, ritonavir was administered at doses of 0, 15, 35, and 60 mg/kg/day from gestation day 6 through postnatal day 20. At doses of 60 mg/kg/day, no developmental toxicity was noted with ritonavir dosage equivalent to 1/2 of the recommended daily dose, based on a body surface area conversion factor.

8.2 Lactation Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. 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, instruct mothers not to breastfeed if they are receiving ritonavir.

8.3 Females and Males of Reproductive Potential

Contraception Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception /see Drug Interactions (7.2).

8.4 Pediatric Use

In HIV-infected patients age greater than 1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

8.5 Geriatric Use

Clinical studies of ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dose adjustment of ritonavir is necessary for natients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) benatic impairment. No pharmacokinetic or safety data are available regarding the use of ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, ritonavir is not recommended for use in patients with severe hepatic impairment (see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)). 10 OVERDOSAGE

Acute Overdosage - Human Overdose Experience

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg per 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 vir oral solution contains alcohol and propylene glycol. Ingestion of the product over the recommended dose by a young child could result in

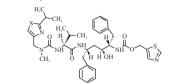
significant toxicity and could potentially be lethal.

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 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. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with ritonavir oral solution. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with ritonavir.

11 DESCRIPTION

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

 $\label{eq:constraints} an initiation of not processes with a control signature number of the number of the second secon$ molecular weight is 720.94. Ritonavir has the following structural formula



Ritonavir, USP is a white to off-white powder. It is freely soluble in methanol, methylene chloride, very slightly soluble in acetonitrile and practically insoluble in water.

Ritonavir tablets, USP are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: colloidal silicon dioxide, copovidone, dibasic calcium phosphate anhydrous, sodium stearyl fumarate and sorbitan monolaurate. The tablets are coated with Opadry White which contains colloidal anhydrous silica, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Ritonavir is an antiretroviral drug*[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Or and a create of the state of with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) time-matched difference in OTEF from placebo after baseline correction was 5.5 (7.6) milliseconds (msec) for 400 mg twice-daily ritonavir. Ritonavir 400 mg twice daily resulted in Day 3 ritonavir exposure that was approximately 1.5 fold higher than observed with ritonavir 600 mg twice-daily dose at steady state.

PR interval prolongation was also noted in subjects receiving ritonavir in the same study on Day 3. The maximum mean (95% confidence interval) difference from placebo in the PR interval after baseline correction was 22 (25) msec for 400 mg twice-daily ritonavir *[see Warnings and Precautions (5.6)]*.

12.3 Pharmacokinetics

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients (CD, greater than or equal to 50 cells per uL). See Table 5 for ritonavir pharmacokinetic characteristics

The absolute bioavailability of ritonavir has not been determined. After a 600 mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting (514 KCal; 9% fat, 12% protein, and 79% carbohydrate) conditions,

Ritonavir tablets are not bioequivalent to ritonavir cansules. Under moderate fat conditions (857 kcal: 31% fat, 13% protein, 56% carbobydrates) The matrix tables are not to equivalent to the matrix of the matrix of

No information is available comparing ritonavir tablets to ritonavir capsules under fasting conditions

Effect of Food on Oral Absorption

The bioavailability of ritonavir tablet and oral solution is decreased under fed conditions as compared to fasted conditions

Following the administration of a 100 mg tablet dose of ritonavir, C_{mat} and AUC_{inf} of ritonavir were decreased by 21 to 23% under moderate fat (857 Kcal. 30% from fat) or high fat conditions (917 Kcal. 60% calories from fat) relative to fasting conditions.

Following the administration of a 600 mg dose ritonavir oral solution, C... and AUC... of ritonavir were decreased by 23% and 7%, respectively, under To normal the community of a contract of the c

| | oo orar olligio aooo | 000 q12.1, 10 u | 8 | ↓ 62% (59, 65%) | (42, 72%) | 110 |
|--------------------------------------|--------------------------------------|---------------------------|------------|-------------------------------------|---------------------------------------|---|
| Normeperidine metabolite | | | 6 | ↑ 47% (-24, 345%) | ↑ 87% (42, 147%) | ND |
| Methadone ² | 5, single dose | 500 q12h, 15 d | 11 | ↓ 36% (16, 52%) | ↓ 38% (28, 46%) | ND |
| Raltegravir | 400, single dose | 100 q12h, 16 d | 10 | ↓ 16% (-30, 1%) | ↓ 24% (-45, 4%) | ↓ 1% (-30, 40%) |
| Rivaroxaban | 10, single dose (days 0 and 7) | 600 q12h (days 2 to 7) | 12 | ↑ 150% (130- 170%) ⁷ | ↑ 60% (40- 70%) ⁷ | ND |
| Rifabutin 25- <i>0</i> -desacetyl | 150 daily, 16 d | 500 q12h, 10 d | 5, | ↑ 4-fold (2.8, 6.1X) | ↑ 2.5-fold (1.9, 3.4X) | ↑ 6-fold (3.5, 18.3X) |
| rifabutin metabolite | | | 11* | ↑ 38-fold | ↑ 16-fold | ↑ 181- |
| | | | | (28, 56X) | (13, 20X) | fold (ND) |
| Sildenafil | 100, single dose | 500 twice daily, 8 d | 28 | ↑ 11-fold | ↑ 4-fold | ND |
| Simeprevir | 200 mg qd, 7 d | 100 mg bid, 15 d | 12 | ↑ 618% (463%- 815%) ⁸ | ↑370% (284%- 476%) ⁸ | ↑1335% (929%- 1901%) ⁸ |
| Sulfamethoxazole ³ | 800, single dose | 500 q12h, 12 d | 15 | ↓ 20% (16, 23%) | \leftrightarrow | ND |
| Tadalafil | 20 mg, single dose | 200 mg q12h | | ↑ 124% | \leftrightarrow | ND |
| Theophylline | 3 mg/kg q8h, 15 d | 500 q12h, 10 d | 13, 11* | ↓ 43% (42, 45%) | ↓ 32% (29, 34%) | ↓57% (55, 59%) |
| Trazodone | 50 mg, single dose | 200 mg q12h, 4 doses | 10 | ↑ 2.4-fold | ↑ 34% | |
| Trimethoprim ³ | 160, single dose | 500 q12h, 12 d | 15 | ↑ 20% (3, 43%) | \leftrightarrow | ND |
| Vardenafil | 5 mg | 600 q12h | | ↑ 49-fold | ↑ 13-fold | ND |
| Voriconazole | 400 q12h, 1 d; then 200 q12h, 8 d | 400 q12h, 9 d | | ↓82% | ↓ 66% | |
| | 400 q12h, 1 d; then 200 q12h, 8 d | 100 q12h, 9 d | | ↓ 39% | ↓ 24% | |
| Warfarin S-Warfarin | 5, single dose | 400 q12h, 12d | 12 | ↑9% (-17, 44%)⁴ | ↓ 9% (-16, -2%) ⁴ | ND |
| R-Warfarin | | | | ↓ 33% (-38, -27%) ⁴ | \leftrightarrow | ND |
| Zidovudine | 200 q8h, 4 d | 300 q6h, 4 d | 9 | ↓ 25% (15, 34%) | ↓ 27% (4, 45%) | ND |

500 q12h, 10 d

200 daily, 7 d

50 oral single dose

ND = not determined

1 Ritonavir and indinavir were co-administered for 15 days; Day 14 doses were administered after a 15%-fat breakfast (757 Kcal) and Section of the sectio

2 Effects were assessed on a dose-normalized comparison to a methadone 20 mg single dose.

3 Sulfamethoxazole and trimethoprim taken as single combination tablet. 4 90% CI presented for R and S-warfarin AUC and Cmax ratios.

5 This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol AUC. 6 For the reference arm: N = 14 for Cmut and AUC (D to inft, and for the test arm: N = 13 for Cmut and N = 4 for AUC(D to inft).

7 90% CI presented for rivaroxaban 8 90% CI presented for simeprevir (change in exposure presented as percentage increase)

↑ Indicates increase, ↓ indicates decrease, ↔indicates no change * Parallel group design; entries are subjects receiving combination and control regimens, respectively.

12.4 Microbiology Mechanism of Action

Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. Inhibition of HIV protease renders the enzyme incapable of processing the Gag-Pol polyprotein precursor which leads to production of non-infectious immature HIV particles.

Antiviral Activity in Cell Culture

The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that The derivity of non-marked seases and the other metric of minimum seases and perpendition of the other seases and the other metric of the other seases and the other metric of the other seases and th didanosine (ddl) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 microM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

Resistance HIV-1 isolates with reduced susceptibility to ritonavir have been selected in cell culture. Genotypic analysis of these isolates showed mutations in the HIV-1 protease gene leading to amino acid substitutions 184V, V82F, A71V, and M46I. Phenotypic (n = 18) and genotypic (n = 48) changes in HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Substitutions asso the HIV-1 viral protease in isolates obtained from 43 patients appeared to occur in a stepwise and ordered fashion at positions V82A/F/T/S, I54V, A71V/T, and I36L, followed by combinations of substitutions at an additional 5 specific amino acid positions (M46I/L, K20R, I84V, L33F and L90M). Of B patients for whom both phenotypic and genotypic analysis were performed on free virus loaded phenotypic and exceptibility to ritonavir in cell culture. All 18 patients possessed one or more substitutions in the viral protease gene. The V82A/F substitution appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to 5-fold decrease in viral sensitivity in cell culture from baselin

Cross-Resistance to Other Antiretrovirals

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV-1 isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in cell culture but did not demonstrate a concordant decrease in susceptibility to saquinavir in cell culture when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in cell culture (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 3 patients had a decrease in susceptibility to nelfinavir (6- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV-1 isolate tested in cell culture retained full susceptibility to ritonavir.

NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

<u>Carcinogenesis</u>

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg per kg per day, there was a dose dependent increase in the increase of the increase of the increase and carcinomas in the liver. Based on ALC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the exposure in humans with the recommended therapeutic dose (600 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 m gper kg per day there were no carcinogenic effects. In this sector were not accounted to be a sector were and the sector were not accounted to be a sector were not account animal studies, the significance of the observed effects is not known.

Mutagenesis

However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Impairment of Fertility

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

14 CLINICAL STUDIES

The activity of ritonavir as monotherapy or in combination with nucleoside reverse transcriptase inhibitors has been evaluated in 1446 patients enrolled in two double-blind, randomized trials.

14.1 Advanced Patients with Prior Antiretroviral Therapy

Study 247 was a randomized, double-bind trial (with open-fabel follow-up) conducted in HIV-infected patients with at least nine months of prior antiretroviral therapy and baseline CD, cell counts less than or equal to 100 cells per μ L. Ritonavir 600 mg twice-daily or placebo was added to each nationt's baseline antiretroviral therany regimen, which could have consisted of up to two approved antiretroviral agents. The study accrued 1,090 patients, with mean baseline CD, cell count at study entry of 32 cells per µL. After the clinical benefit of ritonavir therapy was demonstrated, all patients were eligible to switch to open-label ritonavir for the duration of the follow-up period. Median duration of double-blind therapy with ritonavir and placebo was 6 months. The median duration of follow-up through the end of the open-label phase was 13.5 months for patients randomized to ritonavir and 14 months for patients randomized to placebo.

The cumulative incidence of clinical disease progression or death during the double-blind phase of Study 247 was 26% for patients initially rando to ritonavir compared to 42% for patients initially randomized to placebo. This difference in rates was statistically significan

Cumulative mortality through the end of the open-label follow-up phase for patients enrolled in Study 247 was 18% (99/543) for patients initially randomized to ritonavir compared to 26% (142/547) for natients initially randomized to placebo. This difference in rates was statistically significant However, since the analysis at the end of the open-label phase includes patients in the placebo arm who were switched from placebo to ritonavi therapy, the survival benefit of ritonavir cannot be precisely estimated.

During the double-blind phase of Study 247, CD₄ cell counts increases from baseline for patients randomized to ritonavir at Week 2 and Week 4 were observed. From Week 4 and through Week 24, mean CD, cell counts for patients randomized to ritonavir appeared to plateau. In contrast, there was no d to placabo at any visit botwoo ad Wook 24 of the double

Nearly all of the plasma radioactivity after a single oral 600 mg dose of "C-ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five rearry and the plant abulactory relation of the single of a solution of the solution of solution of a solution of the solution microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M–2.

In a study of five subjects receiving a 600 mg dose of ¹⁴C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

Table 5. Ritonavir Pharmacokinetic Characteristics

| arameter | N | Values (Mean \pm SD) |
|---------------------|----|------------------------|
| ₅/F [*] | 91 | 0.41 ± 0.25 L/kg |
| 5 | | 3 - 5 h |
| L/F SS [†] | 10 | 8.8 ± 3.2 L/h |
| L/F [‡] | 91 | 4.6 ± 1.6 L/h |
| LR | 62 | < 0.1 L/h |
| BC/Plasma Ratio | | 0.14 |
| ercent Bound* | | 98 to 99% |

Study 247.

14.2 Patients without Prior Antiretroviral Therapy

In Study 245, 356 antiretroviral naive HIV infected patients (mean baseline CD4 = 364 cells per µL) were randomized to receive either ritonavi 600 mg twice-daily, zidovudine 200 mg three-times-daily, or a combination of these drugs.

During the double-blind phase of study 245, greater mean CD4 cell count increases were observed from baseline to Week 12 in the ritonavir-con arms compared to the zidovudine arms. Mean CD, cell count changes subsequently appeared to plateau through Week 24 in the ritonavir arm, whereas mean CD₄ cell counts gradually diminished through Week 24 in the zidovudine and ritonavir plus zidovudine arm

Greater mean reductions in plasma HIV-1 RNA levels were observed from baseline to Week 2 for the ritonavir-containing arms compared to the zidovudine arm. After Week 2 and through Week 24, mean plasma HIV-1 RNA levels either remained stable in the ritonavir and zidovudine arms or gradually rebounded toward baseline in the ritonavir plus zidovudine arm.

15 REFERENCES

Sewester CS. Calculations. In: Drug Facts and Comparisons. St. Louis, MO: J.B. Lippincott Co; January, 1997:xix

16 HOW SUPPLIED/STORAGE AND HANDLING

Ritonavir tablets, USP are available in the following strength and package sizes:

Ritonavir Tablets USP, 100 mg Ritonavir USP

Ritonavir tablets, USP are white to off white, capsule shaped, film coated tablets debossed with 'H' on one side and 'R9' on other side.

| Bottles of 30 tablets | NDC 31722-597-30 |
|------------------------|------------------|
| Bottles of 120 tablets | NDC 31722-597-12 |

Recommended Storage Store at or below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for seven days permitted. Dispense in original container or USP