FULL PRESCRIBING INFORMATION

WARNING: DRUG-DRUG INTERACTIONS LEADING TO POTENTIALLY SERIOUS AND/OR LIFE THREATENING REACTIONS

Co-administration of NORVIR 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 NORVIR on the hepatic metabolism of certain drugs. Review medications taken by patients prior to prescribing NORVIR or when prescribing other medications to patients already taking NORVIR *[see Contraindications (4), Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NORVIR tablets and oral solution are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

NORVIR oral powder is indicated in combination with other antiretroviral agents for the treatment of pediatric patients with HIV-1 infection.

2 DOSAGE AND ADMINISTRATION

2.1 General Administration Recommendations

- NORVIR must be used in combination with other antiretroviral agents.
- NORVIR is administered orally. NORVIR tablets should be swallowed whole, and not chewed, broken or crushed. Take NORVIR with meals.
- Patients may improve the taste of NORVIR oral solution by mixing with chocolate milk, Ensure®, or Advera® within one hour of dosing.
- NORVIR oral powder should be mixed with soft food such as apple sauce or vanilla pudding, or mixed with liquid such as water, chocolate milk, or infant formula *[see Dosage and Administration (2.5) and Instructions for Use]*. The bitter aftertaste of NORVIR oral powder may be lessened if administered with food.

General Dosing Guidelines

Patients who take the 600 mg twice daily soft gel capsule NORVIR dose may experience more gastrointestinal side effects such as nausea, vomiting, abdominal pain or diarrhea when switching from the soft gel capsule to the tablet formulation because of greater maximum plasma concentration (C_{max}) achieved with the tablet formulation relative to the soft gel capsule *[see Clinical Pharmacology (12.3)]*. Patients should also be aware that these adverse events (gastrointestinal or paresthesias) may diminish as therapy is continued.

2.2 Administering Oral Solution by Feeding Tube

Because NORVIR oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used for administration of NORVIR oral solution. Follow instructions for use of the feeding tube to administer the medicine.

2.3 Dosage Recommendations in Adults

Recommended Dosage for Treatment of HIV-1:

The recommended dosage of NORVIR is 600 mg twice daily by mouth to be taken with meals. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. NORVIR should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. The maximum dose of 600 mg twice daily should not be exceeded upon completion of the titration *[see Dosage and Administration (2.6)]*.

Pregnant Women

NORVIR oral solution is not recommended during pregnancy due to its ethanol content. NORVIR oral solution contains the excipients ethanol (approx. 43% v/v) and propylene glycol (approx. 27% w/v) *[see Use in Specific Populations (8.1)]*.

2.4 Dosage Recommendations in Pediatric Patients

NORVIR must be used in combination with other antiretroviral agents *[see Dosage and Administration (2)]*. The recommended dosage of NORVIR in pediatric patients older than 1 month is 350 to 400 mg per m^2 twice daily by mouth to be taken with meals and should not exceed 600 mg twice daily. NORVIR should be started at 250 mg per m^2 twice daily and increased at 2 to 3 day intervals by 50 mg per m^2 twice daily. If patients do not tolerate 400 mg per m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered *[see Dosage and Administration (2.6)]*.

Pediatric Dosage Guidelines for Oral Solution

NORVIR oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 44 weeks has been attained *[see Warnings and Precautions (5.2)]*.

NORVIR oral solution contains the excipients ethanol (approx. 43% v/v) and propylene glycol (approx. 27% w/v). Special attention should be given to accurate calculation of the dose of NORVIR, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, and overdose. This is especially important for young children. Total amounts of ethanol and propylene glycol from all medicines that are to be given to pediatric patients 1 to 6 months of age should be taken into account in order to avoid toxicity from these excipients *[see Warnings and Precautions (5.2)* and *Overdosage (10)]*. When possible, dose should be administered using a calibrated dosing syringe.

Table 1. Pediatric Dosage Guidelines for Oral Solution*

Body Surface Area (m^2)	Twice Daily Dose 250 mg per m^2	Twice Daily Dose 300 mg per m^2	Twice Daily Dose 350 mg per m^2	Twice Daily Dose 400 mg per m^2
0.20	0.6 mL (50 mg)	0.75 mL (60 mg)	0.9 mL (70 mg)	1.0 mL (80 mg)
0.25	0.8 mL (62.5 mg)	0.9 mL (75 mg)	1.1 mL (87.5 mg)	1.25 mL (100 mg)
0.50	1.6 mL (125 mg)	1.9 mL (150 mg)	2.2 mL (175 mg)	2.5 mL (200 mg)
0.75	2.3 mL (187.5 mg)	2.8 mL (225 mg)	3.3 mL (262.5 mg)	3.75 mL (300 mg)
1.00	3.1 mL (250 mg)	3.75 mL (300 mg)	4.4 mL (350 mg)	5 mL (400 mg)
1.25	3.9 mL (312.5 mg)	4.7 mL (375 mg)	5.5 mL (437.5 mg)	6.25 mL (500 mg)
1.50	4.7 mL (375 mg)	5.6 mL (450 mg)	6.6 mL (525 mg)	7.5 mL (600 mg)

*The concentration of the oral solution is 80 mg per mL.

Body surface area (BSA) can be calculated as follows[1]:

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (Cm) \times Wt\ (kg)}{3600}}$$

Pediatric Dosage Guidelines for Oral Powder

NORVIR oral powder should be used only for dosing increments of 100 mg. NORVIR powder should not be used for doses less than 100 mg or for incremental doses between 100 mg intervals. NORVIR oral solution is the preferred formulation for patients requiring doses less than 100 mg or incremental doses between 100 mg intervals.

2.5 Preparation of Norvir Oral Powder

For details on the preparation and administration of NORVIR oral powder (see *Instructions for Use*). NORVIR oral powder should only be used for dosing increments of 100 mg.

Prepare the dose using the required number of packets. For example, use one packet for doses of 100 mg and two packets for doses of 200 mg. Pour and mix the entire contents of each packet over soft food or liquid. All of the powder mixed with soft food or liquid should be administered within 2 hours of preparation. If not administered within 2 hours of preparation, the mixture should be discarded and a new dose prepared.

The prescribed dose of NORVIR oral powder can be administered via a feeding tube after being mixed with water (see *Instructions for Use*). Follow the instructions for the feeding tube to administer the medicine.

2.6 Dose Modification due to Drug Interaction

Dose reduction of NORVIR is necessary when used with other protease inhibitors: atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir.

Prescribers should consult the full prescribing information and clinical study information of these protease inhibitors if they are co-administered with a reduced dose of ritonavir *[see Warnings and Precautions (5.1)*, and *Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

- NORVIR Tablets

White film-coated ovaloid tablets debossed with the "a" logo and the code NK providing 100 mg ritonavir.

- NORVIR Oral Solution

Orange-colored liquid containing 600 mg ritonavir per 7.5 mL marked dosage cup (80 mg per mL).

- NORVIR Oral Powder

Beige/pale yellow to yellow powder in child-resistant packet. Each packet contains 100 mg of ritonavir.

4 CONTRAINDICATIONS

- When co-administering NORVIR with other protease inhibitors, see the full prescribing information for that protease inhibitor including contraindication information.
- NORVIR is contraindicated in patients with known hypersensitivity (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir or any of its ingredients.
- NORVIR is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.
  - Alpha 1- Adrenoreceptor Antagonist : alfuzosin
  - Antianginal: ranolazine
  - Antiarrhythmics: amiodarone, dronedarone, flecainide, propafenone, quinidine
  - Antifungal: voriconazole
  - Anti-gout: colchicine
  - Antipsychotics: lurasidone, pimozide
  - Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine
  - GI Motility Agent: cisapride
  - HMG-CoA Reductase Inhibitors: lovastatin, simvastatin
  - Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide
  - PDE5 Inhibitor: sildenafil (Revatio®) when used for the treatment of pulmonary arterial hypertension
  - Sedative/Hypnotics: triazolam, orally administered midazolam

- NORVIR is contraindicated with drugs that are potent CYP3A inducers where significantly reduced ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.
  - Anticancer Agents: apalutamide
  - Herbal Products: St. John's Wort (hypericum perforatum)

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of NORVIR, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving NORVIR, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of NORVIR, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of NORVIR.
- Loss of therapeutic effect of NORVIR and possible development of resistance.

When co-administering NORVIR with other protease inhibitors, see the full prescribing information for that protease inhibitor including important Warnings and Precautions.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during NORVIR therapy; review concomitant medications during NORVIR therapy, and monitor for the adverse reactions associated with the concomitant medications *[see Contraindications (4) and Drug Interactions (7)]*.

5.2 Toxicity in Preterm Neonates

NORVIR oral solution contains the excipients ethanol (approx. 43% v/v) and propylene glycol (approx. 27% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at an increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving lopinavir/ritonavir oral solution which also contains the excipients ethanol and propylene glycol.

NORVIR oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. However, if the benefit of using NORVIR oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related

to NORVIR oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of ethanol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients *[see Dosage and Administration (2.4)* and *Overdosage (10)]*.

5.3 Hepatotoxicity

Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving NORVIR alone or in combination with other antiretroviral drugs (see Table 3). There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering NORVIR to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Increased AST/ALT monitoring should be considered in these patients, especially during the first three months of NORVIR treatment *[see Use in Specific Populations (8.6)]*.

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

5.4 Pancreatitis

Pancreatitis has been observed in patients receiving NORVIR therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis *[see Warnings and Precautions (5.7)]*. Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and NORVIR therapy should be discontinued if a diagnosis of pancreatitis is made.

5.5 Allergic Reactions/Hypersensitivity

Allergic reactions including 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.

NORVIR 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-adrenergic blockers, digoxin and atazanavir) 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 NORVIR therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total cholesterol and triglycerides *[see Adverse Reactions (6.1)]*. Triglyceride and cholesterol testing should be performed prior to initiating NORVIR therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions with NORVIR 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 in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consider monitoring for hyperglycemia, new onset diabetes mellitus, or an exacerbation of diabetes mellitus in patients treated with NORVIR.

5.9 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including NORVIR. During 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 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

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

5.10 Fat Redistribution

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

5.11 Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some

patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.12 Resistance/Cross-resistance

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors *[see Microbiology (12.4)]*.

5.13 Laboratory Tests

Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating NORVIR therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Drug Interactions *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Pancreatitis *[see Warnings and Precautions (5.4)]*
- Allergic Reactions/Hypersensitivity *[see Warnings and Precautions (5.5)]*

When co-administering NORVIR with other protease inhibitors, see the full prescribing information for that protease inhibitor including adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults

The safety of NORVIR alone and in combination with other antiretroviral agents was studied in 1,755 adult patients. Table 2 lists treatment-emergent Adverse Reactions (with possible or probable relationship to study drug) occurring in greater than or equal to 1% of adult patients receiving NORVIR in combined Phase II/IV studies.

The most frequently reported adverse drug reactions among patients receiving NORVIR 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.

Table 2. Treatment-Emergent Adverse Reactions (With Possible or Probable Relationship to Study Drug) Occurring in greater than or equal to 1% of Adult Patients Receiving NORVIR in Combined Phase II/IV Studies (N = 1,755)

Adverse Reactions	n	%
Eye disorders		
Blurred vision	113	6.4
Gastrointestinal disorders		
Abdominal Pain (upper and lower)*	464	26.4
Diarrhea including severe with electrolyte imbalance*	1,192	67.9
Dyspepsia	201	11.5
Flatulence	142	8.1
Gastrointestinal hemorrhage*	41	2.3
Gastroesophageal reflux disease (GERD)	19	1.1
Nausea	1,007	57.4
Vomiting*	559	31.9
General disorders and administration site conditions		
Fatigue including asthenia*	811	46.2
Hepatobiliary disorders		
Blood bilirubin increased (including jaundice)*	25	1.4
Hepatitis (including increased AST, ALT, GGT)*	153	8.7
Immune system disorders		
Hypersensitivity including urticaria and face edema*	114	8.2
Metabolism and nutrition disorders		
Edema and peripheral edema*	110	6.3
Gout*	24	1.4
Hypercholesterolemia*	52	3.0
Hypertriglyceridemia*	158	9.0
Lipodystrophy acquired*	51	2.9
Musculoskeletal and connective tissue disorders		
Arthralgia and back pain*	326	18.6
Myopathy/creatine phosphokinase increased*	66	3.8
Myalgia	156	8.9
Nervous system disorders		
Dizziness*	274	15.6
Dysgeusia*	285	16.2
Paresthesia (including oral paresthesia)*	889	50.7
Peripheral neuropathy	178	10.1
Syncope*	58	3.3
Psychiatric disorders		

Confusion*	52	3.0
Disturbance in attention	44	2.5
Renal and urinary disorders		
Increased urination*	74	4.2
Respiratory, thoracic and mediastinal disorders		
Coughing*	380	21.7
Oropharyngeal Pain*	279	15.9
Skin and subcutaneous tissue disorders		
Acne*	67	3.8
Pruritus*	214	12.2
Rash (includes erythematous and maculopapular)*	475	27.1
Vascular disorders		
Flushing, feeling hot*	232	13.2
Hypertension*	58	3.3
Hypotension including orthostatic hypotension*	30	1.7
Peripheral coldness*	21	1.2
* Represents a medical concept including several similar MedDRA PTs		

Laboratory Abnormalities in Adults

Table 3 shows the percentage of adult patients who developed marked laboratory abnormalities.

Table 3. Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and Hematology Abnormalities Occurring in greater than 3% of Patients Receiving NORVIR

		Study 245 Naive Patients			Study 247 Advanced Patients		Study 462 PI-Naive Patients
Variable	**Limit**	**NORVIR plus ZDV**	**NORVIR**	**ZDV**	**NORVIR**	**Placebo**	**NORVIR plus Saquinavir**
Chemistry	**High**						
Cholesterol	> 240 mg/dL	30.7	44.8	9.3	36.5	8.0	65.2
CPK	> 1000 IU/L	9.6	12.1	11.0	9.1	6.3	9.9
GGT	> 300 IU/L	1.8	5.2	1.7	19.6	11.3	9.2
SGOT (AST)	> 180 IU/L	5.3	9.5	2.5	6.4	7.0	7.8
SGPT (ALT)	> 215 IU/L	5.3	7.8	3.4	8.5	4.4	9.2
Triglycerides	> 800 mg/dL	9.6	17.2	3.4	33.6	9.4	23.4
Triglycerides	> 1500 mg/dL	1.8	2.6	-	12.6	0.4	11.3
Triglycerides Fasting	> 1500 mg/dL	1.5	1.3	-	9.9	0.3	-

Uric Acid	> 12 mg/dL	-	-	-	3.8	0.2	1.4
Hematology	**Low**						
Hematocrit	< 30%	2.6	-	0.8	17.3	22.0	0.7
Hemoglobin	< 8.0 g/dL	0.9	-	-	3.8	3.9	-
Neutrophils	$\leq 0.5 \times 10^9$/L	-	-	-	6.0	8.3	-
RBC	$< 3.0 \times 10^{12}$/L	1.8	-	5.9	18.6	24.4	-
WBC	$< 2.5 \times 10^9$/L	-	0.9	6.8	36.9	59.4	3.5
- Indicates no events reported.							

Adverse Reactions in Pediatric Patients

NORVIR has been studied in 265 pediatric patients greater than 1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in greater than or equal to 2% of pediatric patients enrolled in NORVIR clinical trials.

Laboratory Abnormalities in Pediatric Patients

The following Grade 3-4 laboratory abnormalities occurred in greater than 3% of pediatric patients who received treatment with NORVIR either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (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 NORVIR. 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 NORVIR 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.

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis (TEN) has been reported.

7 DRUG INTERACTIONS

When co-administering NORVIR with other protease inhibitors (atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir), see the full prescribing information for that protease inhibitor including important information for drug interactions.

7.1 Potential for NORVIR to Affect Other Drugs

Ritonavir is an inhibitor of cytochrome P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when co-administered with ritonavir. Thus, co-administration of NORVIR with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 4.

Ritonavir also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

7.2 Established and Other Potentially Significant Drug Interactions

Table 4 provides a list of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction *[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]* for magnitude of interaction.

Table 4. Established and Other Potentially Significant Drug Interactions

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 *[see Contraindications (4)]*.

Antianginal: ranolazine	↑ ranolazine	Contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
Analgesics, Narcotic: tramadol, propoxyphene, methadone, fentanyl	↑ analgesics ↓ methadone ↑ fentanyl	A dose decrease may be needed for these drugs when co-administered with ritonavir. Dosage increase of methadone may be considered. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with NORVIR.
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 ethanol, 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 *[see Contraindications (4)]*.
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, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer agents ↓ ritonavir[#]	Apalutamide is contraindicated due to potential for loss of virologic response and possible resistance to NORVIR or to the class of protease inhibitors *[see Contraindications (4)]*. Avoid co-administration of encorafenib or ivosidenib with NORVIR due to potential risk of serious adverse events such as QT interval prolongation. If co-administration of encorafenib with NORVIR cannot be avoided, modify dose as recommended in encorafenib USPI. If co-administration of ivosidenib with NORVIR cannot be avoided, reduce ivosidenib dose to 250 mg once daily.

		Avoid use of neratinib, venetoclax or ibrutinib with NORVIR. For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when ritonavir is administered concurrently with vincristine or vinblastine. 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 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 dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as NORVIR. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions.
Anticoagulant: warfarin	↑↓ warfarin	Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is recommended.
Anticoagulant: rivaroxaban	↑ rivaroxaban	Avoid concomitant use of rivaroxaban and ritonavir. Co-administration of ritonavir and rivaroxaban may lead to risk of increased bleeding.
Anticonvulsants: carbamazepine, clonazepam, ethosuximide	↑ anticonvulsants	A dose decrease may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Anticonvulsants: divalproex, lamotrigine, phenytoin	↓ anticonvulsants	A dose increase may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available.
Antidepressants: nefazodone, selective serotonin reuptake inhibitors (SSRIs): e.g. fluoxetine,	↑ antidepressants	A dose decrease may be needed for these drugs when co-administered with ritonavir.

paroxetine, tricyclics: e.g. amitriptyline, nortriptyline		
Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Patients receiving ritonavir and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: desipramine	↑ desipramine	Dosage reduction and concentration monitoring of desipramine is recommended.
Antidepressant: trazodone	↑ trazodone	Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and NORVIR. A lower dose of trazodone should be considered.
Antiemetic: dronabinol	↑ dronabinol	A dose decrease of dronabinol may be needed when co-administered with ritonavir.
Antifungals: ketoconazole itraconazole voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole or itraconazole (greater than 200 mg per day) are not recommended. Co-administration of voriconazole and ritonavir doses of 400 mg every 12 hours or greater is contraindicated due to the potential for loss of antifungal response *[see Contraindications (4)]*. Co-administration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Anti-gout: colchicine	↑ colchicine	Contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment *[see Contraindications (4)]*. For patients with normal renal or hepatic function: *Treatment of gout flares-co-administration of colchicine in patients on ritonavir:*0.6 mg (one tablet) for one dose, followed by 0.3 mg (half tablet) one hour later. Dose to be repeated no earlier than three days. *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 adjusted to 0.3 mg once a day.

		If the original colchicine regimen was 0.6 mg 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 in patients on ritonavir:* Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment, adjust clarithromycin dose as follows: • For patients with CL_{CR} 30 to 60 mL per min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} 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.
Antimycobacterial: bedaquiline	↑ bedaquiline	Bedaquiline should only be used with ritonavir if the benefit of co-administration outweighs the risk.
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	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.
Antimycobacterial: rifampin	↓ ritonavir	May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone dose may be needed.
Antiparasitic: quinine	↑ quinine	A dose decrease of quinine may be needed when co-administered with ritonavir.
Antipsychotics: lurasidone	↑ lurasidone	Contraindicated due to potential for serious and/or life-threatening reactions *[see Contraindications (4)]*.
pimozide	↑ pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias *[see Contraindications (4)]*.
Antipsychotics: perphenazine, risperidone, thioridazine	↑ antipsychotics	A dose decrease may be needed for these drugs when co-administered with ritonavir.

Antipsychotics: quetiapine	↑ quetiapine	Initiation of NORVIR in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking NORVIR: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
β-Blockers: metoprolol, timolol	↑ beta-blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir.
Bronchodilator: theophylline	↓ theophylline	Increased dosage of theophylline may be required; therapeutic monitoring should be considered.
Calcium channel blockers: diltiazem, nifedipine, verapamil	↑ calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir.
Digoxin	↑ digoxin	Concomitant administration of ritonavir with digoxin may increase digoxin levels. Caution should be exercised when co-administering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.
Endothelin receptor antagonists: bosentan	↑ bosentan	Co-administration of bosentan in patients on ritonavir: In patients who have been receiving ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Co-administration of ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir.

		After at least 10 days following the initiation of ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
GnRH Receptor Antagonists: elagolix	↑ elagolix ↓ ritonavir	Concomitant use of elagolix 200 mg twice daily and NORVIR for more than 1 month is not recommended due to potential risk of adverse events such as bone loss and hepatic transaminase elevations. Limit concomitant use of elagolix 150 mg once daily and NORVIR to 6 months.
Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system *[see Contraindications (4)]*.
GI Motility Agent: cisapride	↑ cisapride	Contraindicated due to potential for cardiac arrhythmias *[see Contraindications (4)]*.
Hepatitis C direct acting antiviral: glecaprevir/pibrentasvir simeprevir	 ↑ glecaprevir ↑ pibrentasvir ↑simeprevir	It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir, or simeprevir.
Herbal Products: St. John's Wort (hypericum perforatum)	↓ ritonavir	Contraindicated due to potential for loss of virologic response and possible resistance to NORVIR or to the class of protease inhibitors *[see Contraindications (4)]*.
Lipid-modifying agents HMG-CoA Reductase Inhibitor: lovastatin simvastatin	 ↑ lovastatin ↑ simvastatin	 Contraindicated due to potential for myopathy including rhabdomyolysis *[see Contraindications (4)]*.
atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Titrate atorvastatin and rosuvastatin dose carefully and use the lowest necessary dose. If NORVIR is used with another protease inhibitor, see the complete prescribing information for the concomitant protease inhibitor for details on co-administration with atorvastatin and rosuvastatin.

Microsomal triglyceride transfer protein (MTTP) Inhibitor: lomitapide	↑ lomitapide	Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated due to potential for hepatotoxicity *[see Contraindications (4)]*.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin)	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir.
Kinase Inhibitors: fostamatinib *(also see anticancer agents above)*	↑ 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.
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.
Oral Contraceptives or Patch Contraceptives: ethinyl estradiol	↓ ethinyl estradiol	Alternate methods of contraception should be considered.
PDE5 Inhibitors: avanafil sildenafil, tadalafil, vardenafil	↑ avanafil ↑ sildenafil ↑ 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 *[see Contraindications (4)]*. 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 *[see Contraindications (4)]*. 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 one week, 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: Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 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: • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours Use with increased monitoring for adverse events.
Sedative/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotics	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Sedative/Hypnotics: triazolam, orally administered midazolam	↑ triazolam ↑ midazolam	Contraindicated due to potential for prolonged or increased sedation or respiratory depression *[see Contraindications (4)]*.
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.
Stimulant: methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir.
Systemic/Inhaled/ Nasal/Ophthalmic Corticosteroids: e.g., betamethasone budesonide ciclesonide dexamethasone fluticasone methylprednisolone mometasone prednisone triamcinolone	↑ glucocorticoids	Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A 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 CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.
[#] refers to interaction with apalutamide.		

8 USE IN SPECIFIC POPULATIONS

When co-administering NORVIR with other protease inhibitors, see the full prescribing information for the co-administered protease inhibitor including important information for use in special populations.

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NORVIR during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

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 birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *[see Data]*.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with oral administration of ritonavir to pregnant rats and rabbits. During organogenesis in the rat and rabbit, systemic exposure (AUC) was approximately 1/3 lower than human exposure at the

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 NORVIR.

8.3 Females and Males of Reproductive Potential

Contraception

Use of NORVIR 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 NORVIR 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 patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic 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)]*.

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) time-matched difference in QTcF 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_4 greater than or equal to 50 cells per μL). See Table 5 for ritonavir pharmacokinetic characteristics.

Absorption

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, respectively.

NORVIR tablets are not bioequivalent to NORVIR capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg NORVIR dose was administered as a tablet compared with a capsule, $AUC_{(0-\infty)}$ met equivalence criteria but mean C_{max} was increased by 26% (92.8% confidence intervals: ↑15 -↑39%).

No information is available comparing NORVIR tablets to NORVIR capsules under fasting conditions.

After administration of a single 100 mg dose under fed conditions (617 Kcal, 29% calories from fat), NORVIR oral powder demonstrated comparable bioavailability to the oral solution.

Effect of Food on Oral Absorption

The bioavailability of NORVIR tablet, oral solution, and oral powder is decreased under fed conditions as compared to fasted conditions.

Following the administration of a 100 mg tablet dose of NORVIR, C_{max} and AUC_{inf} of ritonavir were decreased by 21-23% 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 NORVIR oral solution, C_{max} and AUC_{inf} of ritonavir were decreased by 23% and 7%, respectively, under nonfasting conditions (514 Kcal, 10% from fat) relative to fasting conditions. Dilution of the oral solution, within one hour of administration, with 240 mL of chocolate milk, Advera® or Ensure® did not significantly affect the extent and rate of ritonavir absorption.

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 inhibits 50% (EC_{50}) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC_{50} value for low passage clinical isolates was 22 nM (n = 13). In MT_4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) 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 I84V, 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 associated with 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 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility 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 baseline.

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.

Instruct 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)]*.

NORVIR tablets and oral solution are manufactured by:
AbbVie Inc.
North Chicago, IL 60064 USA

NORVIR oral powder is manufactured for:
AbbVie Inc.
North Chicago, IL 60064 USA

03-C081

Patient Information

NORVIR® **(NOR-VEER)** (ritonavir) Tablets	**NORVIR®** **(NOR-VEER)** (ritonavir) Oral Solution	**NORVIR®** **(NOR-VEER)** (ritonavir) Oral Powder

What is the most important information I should know about NORVIR?

- NORVIR can interact with other medicines and cause serious side effects. It is important to know the medicines that should not be taken with NORVIR. See the section "Who should not take NORVIR?"

What is NORVIR?

- NORVIR tablets and oral solution are prescription medicines that are used with other antiviral medicines to treat people with human immunodeficiency virus (HIV-1) infection.
- NORVIR oral powder is a prescription medicine that is used with other antiviral medicines to treat children with HIV-1 infection.

HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Do not take NORVIR if you or your child:

- are allergic to ritonavir or any of the ingredients in NORVIR. See the end of this leaflet for a complete list of ingredients in NORVIR.
- If you take any of the following medicines:
- alfuzosin
- apalutamide
- ranolazine
- dronedarone
- colchicine, if you have kidney or liver problems.
- lurasidone
- pimozide
- amiodarone
- ergot-containing medicines including:
- dihydroergotamine mesylate
- ergotamine tartrate
- methylergonovine maleate
- cisapride
- flecainide
- lovastatin
- simvastatin
- lomitapide

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: December 2019
03-C081

Instructions for Use
NORVIR®
(ritonavir)
oral powder

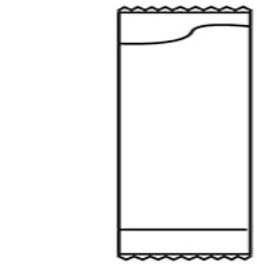
Read these Instructions for Use before you give or take a dose of NORVIR oral powder for the first time and every time you get a new prescription. There may be new information. Talk to your healthcare provider if you have any questions.

Important information

- Your healthcare provider will tell you your dose of NORVIR oral powder and how many packets you will need.
- Each packet contains 100 mg of NORVIR oral powder.
- When you receive your NORVIR oral powder prescription at the pharmacy, check to make sure that the carton is not damaged and that the packets are not opened.
- Check that the expiration date on the carton and packet has not passed.
- Make sure you have enough packets of NORVIR oral powder to give a full dose. Call your healthcare provider if you need more NORVIR oral powder. **Do not run out of your medicine**.
- NORVIR oral powder can be prepared with either food or liquid. **This Instructions for Use is for preparing the dose with food.**
- The food can be replaced with a liquid and the same steps can be followed for preparing a dose.
- If your healthcare provider tells you to give NORVIR oral powder through a feeding tube, **use water to mix NORVIR oral powder**. Follow your healthcare provider's instructions to give the mixture through a feeding tube.
- **Be sure to give or take the entire prepared dose of NORVIR oral powder within 2 hours of preparing the dose.**

For more information about NORVIR oral powder see the Patient Information section of the Prescribing Information.

Items included in the NORVIR oral powder carton



30 Packets of
100 mg NORVIR
oral powder packets

Figure A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

POONAM MISHRA
12/19/2019 12:33:33 PM
on behalf of Debra Birnkrant