HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NORVIR safely and effectively. See full prescribing information for NORVIR.

NORVIR (ritonavir) Tablet for Oral use
NORVIR (ritonavir) Solution for Oral use

Initial U.S. Approval: 1996

WARNING
Co-administration of NORVIR with 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. (4, 5.1)

-------RECENT MAJOR CHANGES-------

Contraindications (4) 12/2011
Warnings and Precautions, Drug Interactions (5.1) 12/2011
Warnings and Precautions, Allergic Reactions (5.4) 12/2011
Warnings and Precautions, Immune Reconstitution Syndrome (5.8) 12/2011

-------INDICATIONS AND USAGE-------

NORVIR is an HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1)

-------DOSAGE AND ADMINISTRATION-------

Take NORVIR with meals (2)
See Full Prescribing Information for complete dosing guidelines.
Dose modification for NORVIR is necessary when used with other protease inhibitors (2)
ADULT PATIENTS (2.1)
600 mg twice-daily with meals.
PEDIATRIC PATIENTS (2.2)
The recommended twice-daily dose for children greater than 1 month of age is based on body surface area and should not exceed 600 mg twice daily with meals.

-------DOSAGE FORMS AND STRENGTHS-------

- Tablet: 100 mg ritonavir (3)
- Oral solution: 80 mg ritonavir per milliliter (3)

-------CONTRAINDICATIONS-------

- NORVIR is contraindicated in patients with known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome) 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)

-------WARNINGS AND PRECAUTIONS-------

The following have been observed in patients receiving NORVIR:

- Drug Interactions: Consider drug-drug interaction potential to reduce risk of serious or life-threatening adverse reactions (5.1)
- Hepatic Reactions: 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 (5.2, 8.6)
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate (5.3)
- 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 (5.4, 6.3)
- 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 (5.5, 12.3)
- Total cholesterol and triglycerides elevations: Monitor prior to therapy and periodically thereafter (5.6)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.7)
- Patients may develop immune reconstitution syndrome (5.8)
- Patients may develop redistribution/accumulation of body fat (5.9)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required (5.10)

-------ADVERSE REACTIONS-------

The most common adverse reactions (> 5% and of moderate to severe intensity) were abdominal pain, asthenia, headache, malaise, anorexia, diarrhea, dyspepsia, nausea, vomiting, paresthesia, circumoral paresthesia, peripheral paresthesia, dizziness, and taste perversion (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-------DRUG INTERACTIONS-------

- Co-administration of NORVIR can alter the concentrations of other drugs. The potential for drug-drug interactions must be considered prior to and during therapy (4, 5.1, 7, 12.3)

-------USE IN SPECIFIC POPULATIONS-------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. Antiretroviral Pregnancy Registry available. Register patients by calling 1–800–258– 4263 (8.1)
- Nursing Mothers: Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving NORVIR (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2011

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FULL PRESCRIBING INFORMATION

WARNING:

Co-administration of NORVIR with 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 *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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.

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.

Dose Modification for NORVIR

Dose reduction of NORVIR is necessary when used with other protease inhibitors: amprenavir, 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)* and *Table 5, Established and Other Potentially Significant Drug Interactions]*.

2.1 Adult Patients

Recommended Dosage for Treatment of HIV-1:

The recommended dosage of ritonavir 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. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3

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day intervals by 100 mg twice daily. The maximum dose of 600 mg twice daily should not be exceeded upon completion of the titration.

2.2 Pediatric Patients

Ritonavir should be used in combination with other antiretroviral agents *[see Dosage and Administration (2)]*. The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m^2 twice daily by mouth to be taken with meals and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2 to 3 day intervals by 50 mg/m^2 twice daily. If patients do not tolerate 400 mg/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. When possible, dose should be administered using a calibrated dosing syringe.

Table 1. Pediatric Dosage Guidelines

Body Surface Area (m^2)	Twice Daily Dose 250 mg/m^2	Twice Daily Dose 300 mg/m^2	Twice Daily Dose 350 mg/m^2	Twice Daily Dose 400 mg/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)

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

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

3 DOSAGE FORMS AND STRENGTHS

- NORVIR Tablets

White film-coated ovaloid tablets debossed with the corporate Abbott "A" logo and the Abbo-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/mL).

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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.
- Co-administration of NORVIR is contraindicated with the drugs listed in Table 2 because ritonavir mediated CYP3A inhibition can result in serious and/or life-threatening reactions. Voriconazole and St. John's Wort are exceptions in that co-administration of NORVIR and voriconazole results in a significant decrease in plasma concentrations of voriconazole, and co-administration of NORVIR with St. John's Wort may result in decreased ritonavir plasma concentrations.

Table 2. Drugs that are Contraindicated with NORVIR

Drug Class	Drugs Within Class That Are Contraindicated With NORVIR**	Clinical Comments:
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Antiarrhythmics	Amiodarone, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias.
Antifungal	Voriconazole	Co-administration of voriconazole with ritonavir 400 mg every 12 hours significantly decreases voriconazole plasma concentrations and may lead to loss of antifungal response. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater *[see Drug Interactions (7.2)]*.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St. John's Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to NORVIR or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors:	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
PDE5 enzyme inhibitor	Sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)	A safe and effective dose has not been established when used with ritonavir. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope *[see Drug Interactions (7.2)]*.
Sedative/hypnotics	Oral midazolam, triazolam	Prolonged or increased sedation or respiratory depression *[see Drug Interactions (7.2)]*.

**see Drug Interactions (7), Table 5* for co-administration of sildenafil in patients with erectile dysfunction.
** For additional information for these contraindicated drugs, *see also Drug Interactions (7), Table 5.*

5 WARNINGS AND PRECAUTIONS

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

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5.1 Drug Interactions

NORVIR is a CYP3A inhibitor. Initiating treatment with NORVIR in patients receiving medications metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already maintained on NORVIR may result in increased plasma concentrations of concomitant medications. Higher plasma concentrations of concomitant medications can result in increased or prolonged therapeutic or adverse effects, potentially leading to severe, life-threatening or fatal events. The potential for drug-drug interactions must be considered prior to and during therapy with NORVIR. Review of other medications taken by patients and monitoring of patients for adverse effects is recommended during therapy with NORVIR.

See Table 2 for a listing of drugs that are contraindicated with NORVIR due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. Also, see Table 5 for a listing of drugs with established and other significant drug interactions *[see Contraindications (4)* and *Drug Interactions (7)]*.

5.2 Hepatic Reactions

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 4). 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.

5.3 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 (5.6)]*. 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.

5.4 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.

5.5 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 Clinical Pharmacology (12.3)]*.

5.6 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)]*.

5.7 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.

5.8 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.

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5.9 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.

5.10 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.

5.11 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 Clinical Pharmacology (12.4)]*.

5.12 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. For comprehensive information concerning laboratory test alterations associated with reverse transcriptase inhibitors, physicians should refer to the complete product information for each of these drugs.

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 (5.2)]*
- Pancreatitis *[see Warnings and Precautions (5.3)]*
- Allergic Reactions/Hypersensitivity *[see Warnings and Precautions (5.4)]*

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.

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

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6.1 Adults - Clinical Trials Experience

The safety of NORVIR alone and in combination with nucleoside reverse transcriptase inhibitors was studied in 1270 adult patients. Table 3 lists treatment-emergent adverse events (at least possibly related and of at least moderate intensity) that occurred in 2% or greater of adult patients receiving NORVIR alone or in combination with nucleoside reverse transcriptase inhibitors in Study 245 or Study 247 and in combination with saquinavir in study 462. In that study, 141 protease inhibitor-naive, HIV-infected patients with mean baseline CD_4 of 300 cells/µL were randomized to one of four regimens of NORVIR + saquinavir, including NORVIR 400 mg twice-daily + saquinavir 400 mg twice-daily. Overall the most frequently reported clinical adverse events, other than asthenia, among adult patients receiving NORVIR were gastrointestinal and neurological disturbances including nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion, and circumoral and peripheral paresthesias. Similar adverse event profiles were reported in adult patients receiving ritonavir in other trials.

Table 3. Percentage of Patients with Treatment-emergent Adverse Events[1] of Moderate or Severe Intensity Occurring in ≥ 2% of Adult Patients Receiving NORVIR

Adverse Events	Study 245 Naive Patients[2]			Study 247 Advanced Patients[3]		Study 462 PI-Naive Patients[4]
	NORVIR + ZDV n = 116	NORVIR n = 117	ZDV n = 119	NORVIR n = 541	Placebo n = 545	NORVIR + Saquinavir n= 141
Body as a Whole						
Abdominal Pain	5.2	6.0	5.9	8.3	5.1	2.1
Asthenia	28.4	10.3	11.8	15.3	6.4	16.3
Fever	1.7	0.9	1.7	5.0	2.4	0.7
Headache	7.8	6.0	6.7	6.5	5.7	4.3
Malaise	5.2	1.7	3.4	0.7	0.2	2.8
Pain (unspecified)	0.9	1.7	0.8	2.2	1.8	4.3
Cardiovascular						
Syncope	0.9	1.7	0.8	0.6	0.0	2.1
Vasodilation	3.4	1.7	0.8	1.7	0.0	3.5
Digestive						
Anorexia	8.6	1.7	4.2	7.8	4.2	4.3
Constipation	3.4	0.0	0.8	0.2	0.4	1.4
Diarrhea	25.0	15.4	2.5	23.3	7.9	22.7
Dyspepsia	2.6	0.0	1.7	5.9	1.5	0.7
Fecal Incontinence	0.0	0.0	0.0	0.0	0.0	2.8
Flatulence	2.6	0.9	1.7	1.7	0.7	3.5
Local Throat Irritation	0.9	1.7	0.8	2.8	0.4	1.4
Nausea	46.6	25.6	26.1	29.8	8.4	18.4
Vomiting	23.3	13.7	12.6	17.4	4.4	7.1
Metabolic and Nutritional						
Weight Loss	0.0	0.0	0.0	2.4	1.7	0.0
Musculoskeletal						
Arthralgia	0.0	0.0	0.0	1.7	0.7	2.1
Myalgia	1.7	1.7	0.8	2.4	1.1	2.1
Nervous						
Anxiety	0.9	0.0	0.8	1.7	0.9	2.1

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Circumoral Paresthesia	5.2	3.4	0.0	6.7	0.4	6.4
Confusion	0.0	0.9	0.0	0.6	0.6	2.1
Depression	1.7	1.7	2.5	1.7	0.7	7.1
Dizziness	5.2	2.6	3.4	3.9	1.1	8.5
Insomnia	3.4	2.6	0.8	2.0	1.8	2.8
Paresthesia	5.2	2.6	0.0	3.0	0.4	2.1
Peripheral Paresthesia	0.0	6.0	0.8	5.0	1.1	5.7
Somnolence	2.6	2.6	0.0	2.4	0.2	0.0
Thinking Abnormal	2.6	0.0	0.8	0.9	0.4	0.7
Respiratory						
Pharyngitis	0.9	2.6	0.0	0.4	0.4	1.4
Skin and Appendages						
Rash	0.9	0.0	0.8	3.5	1.5	0.7
Sweating	3.4	2.6	1.7	1.7	1.1	2.8
Special Senses						
Taste Perversion	17.2	11.1	8.4	7.0	2.2	5.0
Urogenital						
Nocturia	0.0	0.0	0.0	0.2	0.0	2.8

1 Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.
2 The median duration of treatment for patients randomized to regimens containing NORVIR in Study 245 was 9.1 months.
3 The median duration of treatment for patients randomized to regimens containing NORVIR in Study 247 was 9.4 months.
4 The median duration of treatment for patients in Study 462 was 48 weeks.

Adverse events occurring in less than 2% of adult patients receiving NORVIR in all phase II/phase III studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate intensity are listed below by body system.

Body as a Whole

Abdomen enlarged, accidental injury, allergic reaction, back pain, cachexia, chest pain, chills, facial edema, facial pain, flu syndrome, hormone level altered, hypothermia, kidney pain, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and substernal chest pain.

Cardiovascular System

Cardiovascular disorder, cerebral ischemia, cerebral venous thrombosis, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia and vasospasm.

Digestive System

Abnormal stools, bloody diarrhea, cheilitis, cholestatic jaundice, colitis, dry mouth, dysphagia, eructation, esophageal ulcer, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, hepatic coma, hepatitis, hepatomegaly, hepatosplenomegaly, ileus, liver damage, melena, mouth ulcer, pancreatitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, sialadenitis, stomatitis, tenesmus, thirst, tongue edema, and ulcerative colitis.

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Endocrine System

Adrenal cortex insufficiency and diabetes mellitus.

Hemic and Lymphatic System

Acute myeloblastic leukemia, anemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, myeloproliferative disorder, and thrombocytopenia.

Metabolic and Nutritional Disorders

Albuminuria, alcohol intolerance, avitaminosis, BUN increased, dehydration, edema, enzymatic abnormality, glycosuria, gout, hypercholesteremia, peripheral edema, and xanthomatosis.

Musculoskeletal System

Arthritis, arthrosis, bone disorder, bone pain, extraocular palsy, joint disorder, leg cramps, muscle cramps, muscle weakness, myositis, and twitching.

Nervous System

Abnormal dreams, abnormal gait, agitation, amnesia, aphasia, ataxia, coma, convulsion, dementia, depersonalization, diplopia, emotional lability, euphoria, grand mal convulsion, hallucinations, hyperesthesia, hyperkinesia, hypesthesia, incoordination, libido decreased, manic reaction, nervousness, neuralgia, neuropathy, paralysis, peripheral neuropathic pain, peripheral neuropathy, peripheral sensory neuropathy, personality disorder, sleep disorder, speech disorder, stupor, subdural hematoma, tremor, urinary retention, vertigo, and vestibular disorder.

Respiratory System

Asthma, bronchitis, dyspnea, epistaxis, hiccup, hypoventilation, increased cough, interstitial pneumonia, larynx edema, lung disorder, rhinitis, and sinusitis.

Skin and Appendages

Acne, contact dermatitis, dry skin, eczema, erythema multiforme, exfoliative dermatitis, folliculitis, fungal dermatitis, furunculosis, maculopapular rash, molluscum contagiosum, onychomycosis, pruritus, psoriasis, pustular rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin melanoma, urticaria, and vesiculobullous rash.

Special Senses

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

Urogenital System

Acute kidney failure, breast pain, cystitis, dysuria, hematuria, impotence, kidney calculus, kidney failure, kidney function abnormal, kidney pain, menorrhagia, penis disorder, polyuria, urethritis, urinary frequency, urinary tract infection, and vaginitis.

Laboratory Abnormalities

Table 4 shows the percentage of adult patients who developed marked laboratory abnormalities.

Table 4. Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and Hematology Abnormalities Occurring in > 3% of Patients Receiving NORVIR

		Study 245 Naive Patients			Study 247 Advanced Patients		Study 462 PI-Naive Patients
Variable	**Limit**	**NORVIR + ZDV**	**NORVIR**	**ZDV**	**NORVIR**	**Placebo**	**NORVIR + 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.							

6.2 Pediatrics - Treatment-Emergent Adverse Events

NORVIR has been studied in 265 pediatric patients > 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 ≥ 2% of pediatric patients enrolled in NORVIR clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in > 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%).

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6.3 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, 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 (5.5)]*.

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.

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

See also Contraindications (4) , Clinical Pharmacology (12.3)

When co-administering NORVIR with other protease inhibitors (amprenavir, 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 has been found to be 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 (> 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 5.

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.

7.2 Established and Other Potentially Significant Drug Interactions

Table 5 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 Clinical Pharmacology (12.3) for magnitude of interaction]*.

Table 5. 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 Protease Inhibitor: atazanavir	When co-administered with reduced doses of atazanavir and ritonavir ↑ atazanavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	Atazanavir plasma concentrations achieved with atazanavir 300 mg q.d. and ritonavir 100 mg q.d. are higher than those achieved with atazanavir 400 mg q.d. See the complete prescribing information for Reyataz® (atazanavir) for details on co-administration of atazanavir 300 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: darunavir	When co-administered with reduced doses of ritonavir ↑ darunavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Prezista® (darunavir) for details on co-administration of darunavir 600 mg b.i.d. with ritonavir 100 mg b.i.d. or darunavir 800 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: fosamprenavir	When co-administered with reduced doses of ritonavir ↑ amprenavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Lexiva® (fosamprenavir) for details on co-administration of fosamprenavir 700 mg b.i.d. with ritonavir 100 mg b.i.d., fosamprenavir 1400 mg q.d. with ritonavir 200 mg q.d. or fosamprenavir 1400 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: indinavir	When co-administered with reduced doses of indinavir and ritonavir ↑ indinavir (↔ AUC, ↓ C_{max}, ↑ C_{min})	Alterations in concentrations are noted when reduced doses of indinavir are co-administered with NORVIR. Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
HIV Protease Inhibitor: saquinavir	When co-administered with reduced doses of ritonavir ↑ saquinavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Invirase® (saquinavir) for details on co-administration of saquinavir 1000 mg b.i.d with ritonavir 100 mg b.i.d. Saquinavir/ritonavir should not be given together with rifampin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three drugs are given together.
HIV Protease Inhibitor: tipranavir	When co-administered with reduced doses of ritonavir	See the complete prescribing information for Aptivus® (tipranavir) for details

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	↑ tipranavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	on co-administration of tipranavir 500 mg b.i.d. with ritonavir 200 mg b.i.d. There have been reports of clinical hepatitis and hepatic decompensation including some fatalities. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment.
Non-Nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ ritonavir (↑AUC, ↑C_{max}, ↑ C_{min})	Appropriate doses of this combination with respect to safety and efficacy have not been established.
HIV CCR5 – antagonist: maraviroc	↑ maraviroc	Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. For specific dosage adjustment recommendations, please refer to the complete prescribing information for Selzentry® (maraviroc).
Other Agents		
Analgesics, Narcotic: tramadol, propoxyphene		A dose decrease may be needed for these drugs when co-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: disopyramide, lidocaine, mexiletine	↑antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with ritonavir, if available.
Anticancer Agents: dasatinib, nilotinib, vincristine, vinblastine	↑ anticancer agents	Concentrations of these drugs may be increased when co-administered with ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. 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	↓ R-warfarin ↓↑ S-warfarin	Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated.
Anticonvulsants: carbamazepine, clonazepam, ethosuximide	↑anticonvulsants	Use with caution. 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	Use with caution. 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, paroxetine, tricyclics: e.g. amitriptyline, nortriptyline	↑antidepressants	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Antidepressant:	↓ bupropion	Concurrent administration of bupropion with ritonavir may decrease plasma

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bupropion	↓ active metabolite, hydroxybupropion	levels of both bupropion and its 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	Concomitant use of trazodone and NORVIR increases plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and NORVIR. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Antiemetic: dronabinol	↑ dronabinol	A dose decrease of dronabinol may be needed when co-administered with ritonavir.
Antifungal: ketoconazole itraconazole voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole and ritonavir doses of 400 mg every 12 hours or greater is contraindicated. 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	Patients with renal or hepatic impairment should not be given colchicine with ritonavir. <u>Treatment of gout flares-co-administration of colchicine in patients on ritonavir:</u> 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days. <u>Prophylaxis of gout flares-co-administration of colchicine in patients on ritonavir:</u> 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. <u>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on ritonavir:</u> 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 the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antimycobacterial: rifabutin	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (e.g., 150 mg every other day or three times a week). Further dosage reduction may be necessary.
Antimycobacterial: rifampin	↓ ritonavir	May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered (see Antimycobacterial: rifabutin, for dose reduction recommendations).
Antiparasitic:	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone dose may

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atovaquone		be needed.
Antiparasitic: quinine	↑ quinine	A dose decrease of quinine may be needed when co-administered with ritonavir.
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	<u>Co-administration of bosentan in patients on ritonavir:</u> 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. <u>Co-administration of ritonavir in patients on bosentan:</u> 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.
HMG-CoA Reductase Inhibitor: 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.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin)	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir.
Inhaled Steroid: Fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and NORVIR increases plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone propionate and NORVIR is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
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.
Narcotic Analgesic: methadone fentanyl	↓ methadone ↑ fentanyl	Dosage increase of methadone may be considered. Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with NORVIR.
Neuroleptics: perphenazine, risperidone, thioridazine	↑ neuroleptics	A dose decrease may be needed for these drugs when co-administered with ritonavir.
Oral Contraceptives or Patch Contraceptives: ethinyl estradiol	↓ ethinyl estradiol	A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg q. 12h. and a fixed-combination oral contraceptive resulted in reductions of the ethinyl estradiol mean C_{max} and mean AUC by 32% and 40%, respectively. Alternate methods of contraception should be considered.
PDE5 Inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil in patients receiving ritonavir. Co-administration of ritonavir with these drugs is expected to substantially increase their concentrations and 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 when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with ritonavir *[see Contraindications (4)]*. The following dose adjustments are recommended for use of tadalafil (Adcirca™) with ritonavir: <u>Co-administration of ADCIRCA in patients on ritonavir:</u> 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. <u>Co-administration of ritonavir in patients on ADCIRCA:</u> 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: Parenteral midazolam	↑ midazolam	Co-administration of oral midazolam with NORVIR is CONTRAINDICATED. Concomitant use of parenteral midazolam with NORVIR may increase plasma concentrations of 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.
Steroids: dexamethasone, fluticasone, prednisone		A dose decrease may be needed for these drugs when co-administered with ritonavir.
Stimulant: methamphetamine	↑ methamphetamine	Use with caution. A dose decrease of methamphetamine may be needed when co-administered with ritonavir.

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 Category B

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There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No treatment related malformations were observed when ritonavir was administered to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage at an exposure equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cryptorchidism was also noted in rats at an exposure approximately 22% of that achieved with the proposed therapeutic dose.

Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage equivalent to 1.8 times the proposed therapeutic dose based on a body surface area conversion factor.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to NORVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1–800–258–4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether ritonavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving NORVIR.

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 or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of ritonavir in subjects with severe hepatic impairment, therefore, ritonavir is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Acute Overdosage - Human Overdose Experience

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

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

10.2 Management of Overdosage

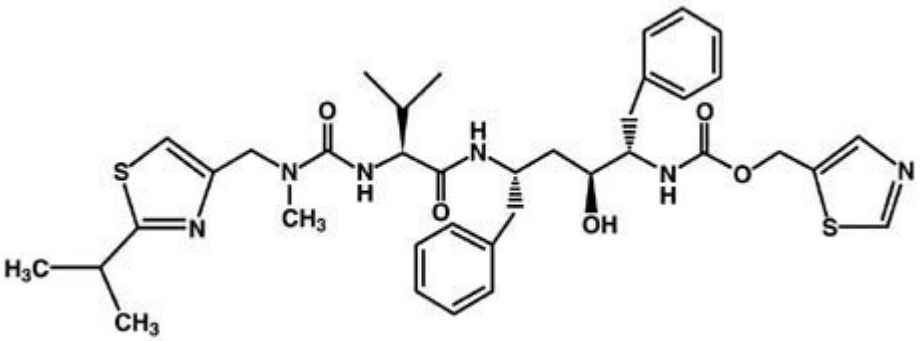
NORVIR oral solution contains 43% alcohol by volume. Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Treatment of overdose with NORVIR 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 NORVIR. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with NORVIR.

11 DESCRIPTION

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

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12- tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is C37H48N6O5S2, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is a white-to-light-tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

NORVIR tablets are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, polyethylene glycol 3350, colloidal silicon dioxide, and polysorbate 80.

NORVIR oral solution is available for oral administration as 80 mg/mL of ritonavir in a peppermint and caramel flavored vehicle. Each 8-ounce bottle contains 19.2 grams of ritonavir. NORVIR oral solution also contains ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C Yellow No. 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ritonavir is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients (CD_4 ≥50 cells/µL). See Table 6 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.

Effect of Food on Oral Absorption

When the oral solution was given under non-fasting conditions, peak ritonavir concentrations decreased 23% and the extent of absorption decreased 7% 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. Administration of a single 600 mg dose oral solution under non-fasting conditions yielded mean ± SD areas under the plasma concentration-time curve (AUCs) of 129.0 ± 39.3 mg•h/mL.

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A food effect is observed for NORVIR tablets. Food decreased the bioavailability of the ritonavir tablets when a single 100 mg dose of NORVIR was administered. Under high fat conditions (907 kcal; 52% fat, 15% protein, 33% carbohydrates), a 23% decrease in mean AUC(0-∞) [90% confidence intervals: ↓30%-↓15%], and a 23% decrease in mean C_{max} [90% confidence intervals: ↓34%-↓11%]) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in mean AUC(0-∞) [90% confidence intervals: ↓28%-↓13%], and a 22% decrease in mean C_{max} [90% confidence intervals: ↓33%-↓9%]) was observed relative to fasting conditions.

However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals.

Metabolism

Nearly all of the plasma radioactivity after a single oral 600 mg dose of ^{14}C-ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. *In vitro* studies utilizing human liver 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.

Elimination

In a study of five subjects receiving a 600 mg dose of ^{14}C-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 6. Ritonavir Pharmacokinetic Characteristics

Parameter	N	Values (Mean ± SD)
C_{max} SS†	10	11.2 ± 3.6 µg/mL
C_{trough} SS†	10	3.7 ± 2.6 µg/mL
V_{β}/F‡	91	0.41 ± 0.25 L/kg
$t_{½}$		3 - 5 h
CL/F SS†	10	8.8 ± 3.2 L/h
CL/F‡	91	4.6 ± 1.6 L/h
CL_R	62	< 0.1 L/h
RBC/Plasma Ratio		0.14
Percent Bound*		98 to 99%

† SS = steady state; patients taking ritonavir 600 mg q12h.
‡ Single ritonavir 600 mg dose.
* Primarily bound to human serum albumin and alpha-1 acid glycoprotein over the ritonavir concentration range of 0.01 to 30 µg/mL.

Effects on Electrocardiogram

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)]*.

Special Populations

Gender, Race and Age

No age-related pharmacokinetic differences have been observed in adult patients (18 to 63 years). Ritonavir pharmacokinetics have not been studied in older patients.

A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir. Pharmacokinetic differences due to race have not been identified.

Pediatric Patients

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m^2 twice-daily to 400 mg/m^2 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/m^2 twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m^2) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m^2 twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m^2) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m^2 twice-daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m^2 twice-daily compared to the 350 mg/m^2 twice-daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice-daily. The area under the ritonavir plasma concentration time curve and trough concentrations obtained after administration with 350 or 450 mg/m^2 twice-daily in children < 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

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Renal Impairment

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

Hepatic Impairment

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

Drug Interactions

[see also Contraindications (4) and *Warnings and Precautions (5.1)]*

Table 7 and Table 8 summarize the effects on AUC and C_{max}, with 95% confidence intervals (95% CI), of co-administration of ritonavir with a variety of drugs. For information about clinical recommendations see Table 5 in *Drug Interactions (7).*

Table 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 NORVIR (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	↔	↔	↔
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%)	↔	ND
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 18% (-3, 52%)	↑ 10% (-11, 36%)	ND
Rifampin	600 or 300 daily, 10 d	500 q12h, 20 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		↔	↔	ND
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	10	↔	↔	↔

Table 8. Drug Interactions - Pharmacokinetic Parameters for Co-administered Drug in the Presence of NORVIR

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of NORVIR (mg)	N	AUC % (95% CI)	C_{max} (95% CI)	C_{min} (95% CI)
Alprazolam	1, single dose	500 q12h, 10 d	12	↓ 12% (-5,30%)	↓ 16% (5, 27%)	ND
Clarithromycin	500 q12h, 4 d	200 q8h, 4 d	22	↑ 77% (56, 103%)	↑ 31% (15, 51%)	↑ 2.8-fold (2.4, 3.3X)
14-OH clarithromycin				↓ 100%	↓ 99%	

metabolite						↓ 100%
Desipramine 2-OH desipramine metabolite	100, single dose	500 q12h, 12 d	14	↑ 145% (103, 211%) ↓ 15% (3, 26%)	↑ 22% (12, 35%) ↓ 67% (62, 72%)	ND ND
Didanosine	200 q12h, 4 d	600 q12h, 4 d	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)	↔
Ethinyl estradiol	50 µg single dose	500 q12h, 16 d	23	↓ 40% (31, 49%)	↓ 32% (24, 39%)	ND
Fluticasone propionate aqueous nasal spray	200 mcg qd, 7 d	100 mg q12h, 7 d	18	↑ approximately 350-fold[5]	↑ approximately 25-fold[5]	
Indinavir[1] Day 14 Day 15	400 q12h, 15 d	400 q12h, 15 d	10	↑ 6% (-14, 29%) ↓ 7% (-22, 28%)	↓ 51% (40, 61%) ↓ 62% (52, 70%)	↑ 4-fold (2.8,6.8X) ↑ 4-fold (2.5,6.5X)
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 3.4-fold (2.8, 4.3X)	↑ 55% (40, 72%)	ND
Meperidine Normeperidine metabolite	50 oral single dose	500 q12h, 10 d	8 6	↓ 62% (59, 65%) ↑ 47% (-24, 345%)	↓ 59% (42, 72%) ↑ 87% (42, 147%)	ND ND
Methadone[2]	5, single dose	500 q12h, 15 d	11	↓ 36% (16, 52%)	↓ 38% (28, 46%)	ND
Rifabutin 25-*O*-desacetyl rifabutin metabolite	150 daily, 16 d	500 q12h, 10 d	5, 11*	↑ 4-fold (2.8, 6.1X) ↑ 38-fold (28, 56X)	↑ 2.5-fold (1.9, 3.4X) ↑ 16-fold (13, 20X)	↑ 6-fold (3.5, 18.3X) ↑ 181-fold (ND)
Sildenafil	100, single dose	500 BID, 8 d	28	↑ 11-fold	↑ 4-fold	ND
Sulfamethoxazole[3]	800, single dose	500 q12h, 12 d	15	↓ 20% (16, 23%)	↔	ND
Tadalafil	20 mg, single dose	200 mg q12h		↑ 124%	↔	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%)	↔	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 R-Warfarin	5, single dose	400 q12h, 12d	12	↑ 9% (-17, 44%)[4] ↓ 33% (-38, -27%)[4]	↓ 9% (-16, -2%)[4] ↔	ND ND
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	9	↓ 25% (15, 34%)	↓ 27% (4, 45%)	ND

1 Ritonavir and indinavir were co-administered for 15 days; Day 14 doses were administered after a 15%-fat breakfast (757 Kcal) and 9%-fat evening snack (236 Kcal), and Day 15 doses were administered after a 15%-fat breakfast (757 Kcal) and 32%-fat dinner (815 Kcal). Indinavir C_{min} was also increased 4-fold. Effects were assessed relative to an indinavir 800 mg q8h regimen under fasting conditions.
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 C_{max} ratios.
5 This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol AUC.
↑ 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}) 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 > 20 µM 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 ≥ 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. 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.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC 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 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of in *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.

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 NORVIR 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-blind trial (with open-label follow-up) conducted in HIV-infected patients with at least nine months of prior antiretroviral therapy and baseline CD_4 cell counts ≤100 cells/µL. NORVIR 600 mg twice-daily or placebo was added to each patient's baseline antiretroviral therapy regimen, which could have consisted of up to two approved antiretroviral agents. The study accrued 1090 patients, with mean baseline CD_4 cell count at study entry of 32 cells/µL. After the clinical benefit of NORVIR therapy was demonstrated, all patients were eligible to switch to open-label NORVIR for the duration of the follow-up period. Median duration of double-blind therapy with NORVIR 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 NORVIR 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 randomized to NORVIR compared to 42% for patients initially randomized to placebo. This difference in rates was statistically significant (see Figure 1).

Figure 1. Time to Disease Progression or Death During the Double-blind Phase of Study 247

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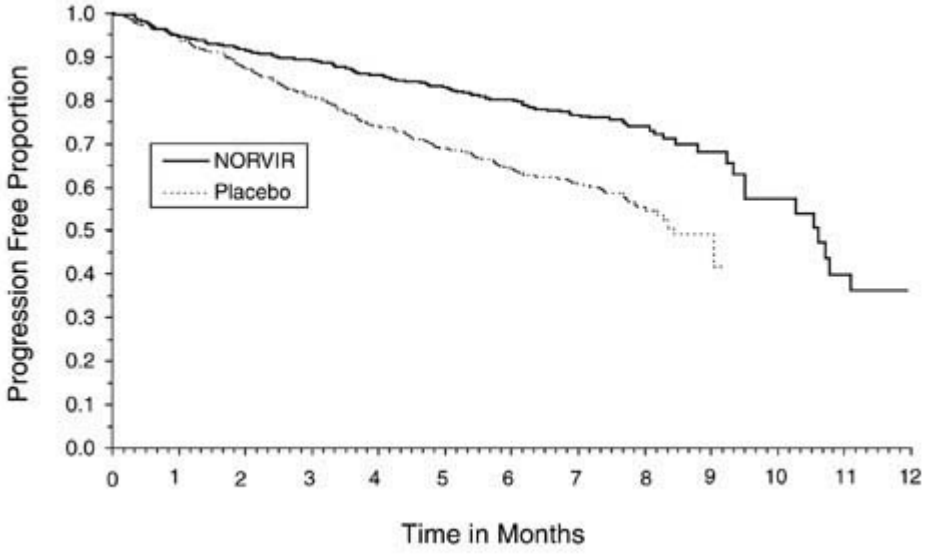


The cumulative mortality through the end of the open-label follow-up phase for patients enrolled in Study 247 was 18% for patients initially randomized to NORVIR compared to 26% for patients initially randomized to placebo. This difference in rates was statistically significant (see Figure 2). Since the analysis at the end of the open-label phase includes patients in the placebo arm who were switched from placebo to NORVIR therapy, the survival benefit of NORVIR cannot be precisely estimated.

Figure 2. Survival of Patients by Randomized Regimen in Study 247

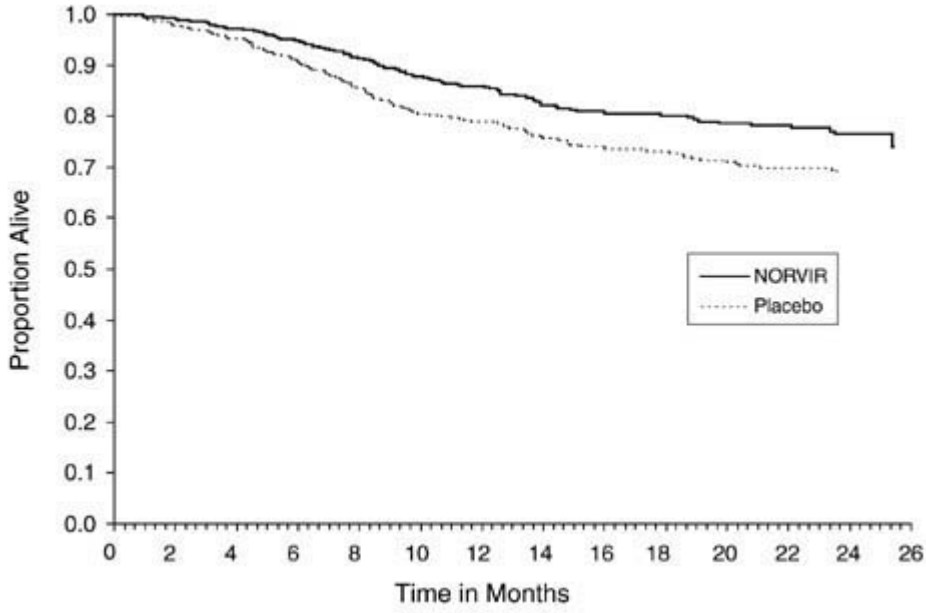


Figure 3 and Figure 4 summarize the mean change from baseline for CD_4 cell count and plasma HIV RNA (copies/mL), respectively, during the first 24 weeks for the double-blind phase of Study 247.

Figure 3. Mean Change from Baseline in CD_4 Cell Count (cells/µL) During the Double-blind Phase of Study 247

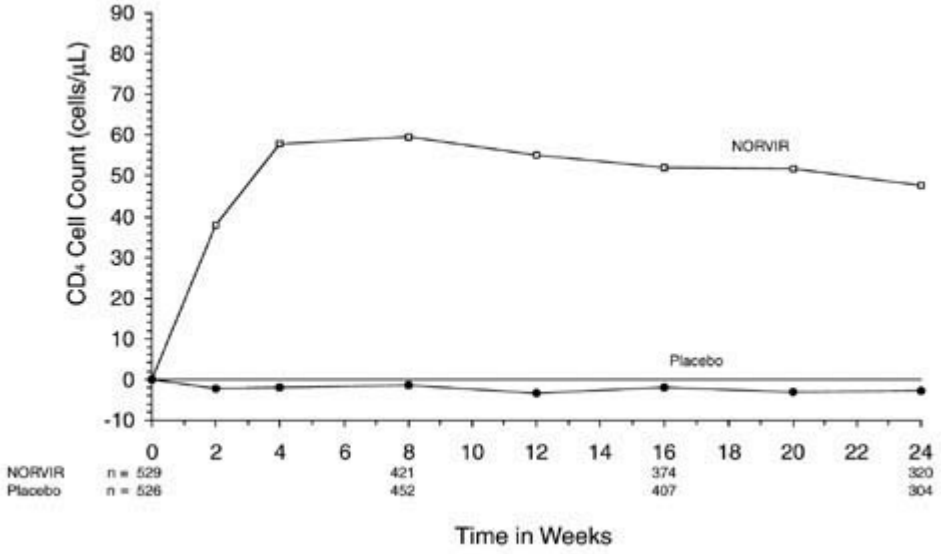
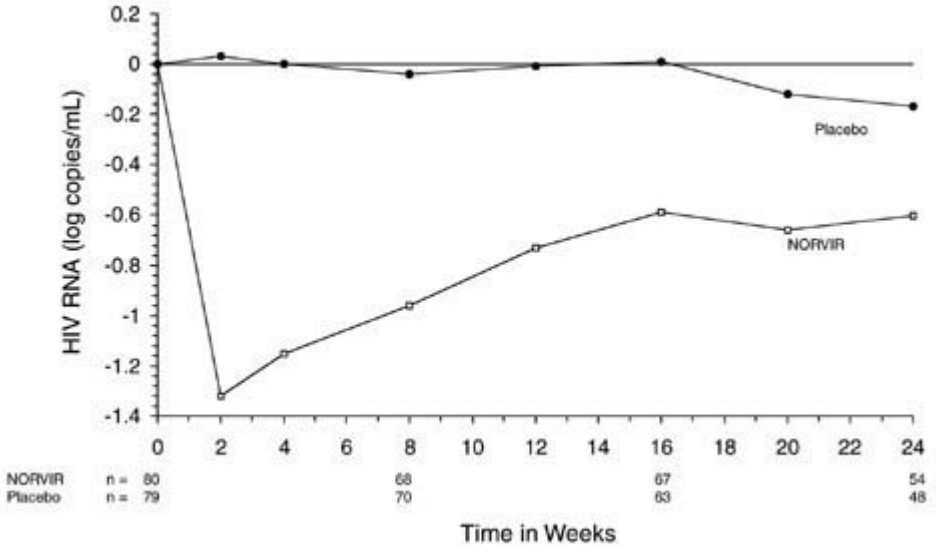


Figure 4. Mean Change from Baseline in HIV RNA (log copies/mL) During the Double-blind Phase of Study 247



14.2 Patients without Prior Antiretroviral Therapy

In Study 245, 356 antiretroviral-naive HIV-infected patients (mean baseline CD_4 = 364 cells/µL) were randomized to receive either NORVIR 600 mg twice-daily, zidovudine 200 mg three-times-daily, or a combination of these drugs. Figure 5 and Figure 6 summarize the mean change from baseline for CD_4 cell count and plasma HIV RNA (copies/mL), respectively, during the first 24 weeks for the double-blind phase of Study 245.

Figure 5. Mean Change from Baseline in CD_4 Cell Count (cells/µL) During Study 245

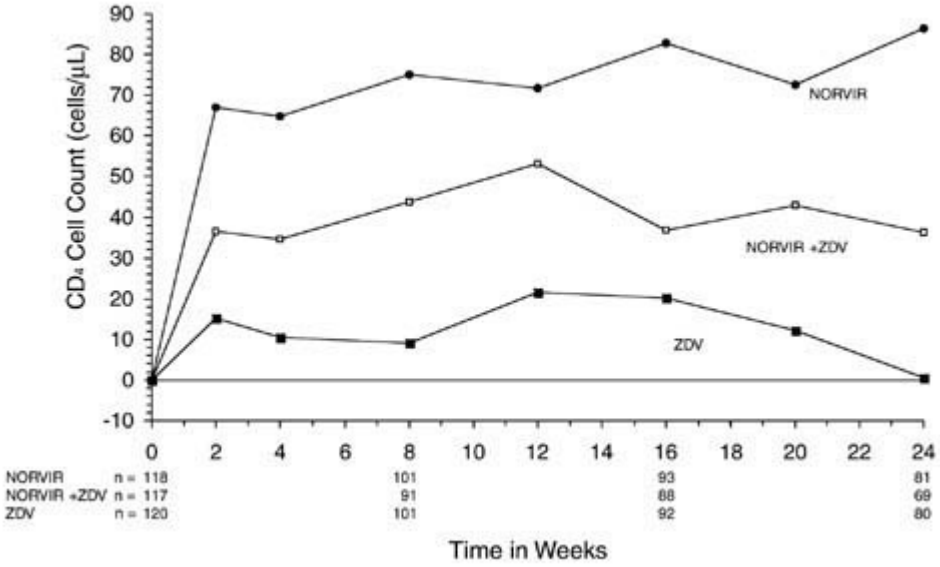
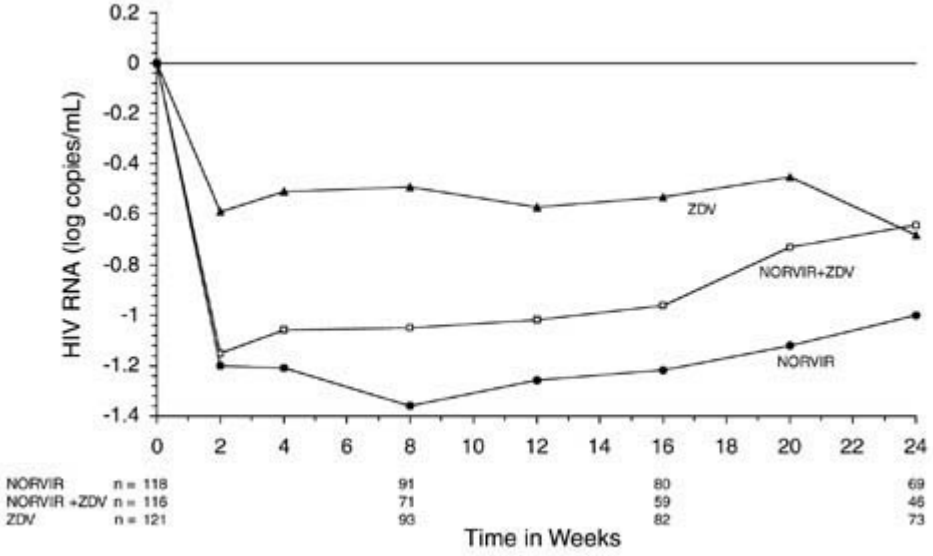


Figure 6. Mean Change from Baseline in HIV RNA (log copies/mL) During Study 245



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

NORVIR (ritonavir) tablets and NORVIR (ritonavir) oral solution are available in the following strengths and package sizes:

16.1 NORVIR Tablets, 100 mg Ritonavir

NORVIR (ritonavir) tablets are white film-coated ovaloid tablets debossed with the corporate Abbott "A" logo and the Abbo-Code NK.

Bottles of 30 tablets each (**NDC** 0074-3333-30).

Recommended Storage

Store NORVIR film-coated tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Dispense in original container or USP 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 recommended.

16.2 NORVIR Oral Solution, 80 mg/mL Ritonavir

NORVIR (ritonavir) oral solution is an orange-colored liquid, supplied in amber-colored, multi-dose bottles containing 600 mg ritonavir per 7.5 mL marked dosage cup (80 mg/mL).

240 mL bottles (**NDC** 0074-1940-63).

Recommended Storage

Store NORVIR oral solution at room temperature 20°-25°C (68°-77°F). Do not refrigerate. Shake well before each use. Use by product expiration date.

Product should be stored and dispensed in the original container.

Avoid exposure to excessive heat. Keep cap tightly closed.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Information For Patients

Patients or parents of patients should be informed that:

General Information

 They should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of NORVIR.

 They should inform their healthcare provider if their children's weight changes in order to make sure that the child's NORVIR dose is the correct one.

 Take NORVIR with meals.

 For adult patients taking NORVIR tablets, the maximum dose of 600 mg twice daily by mouth with meals should not be exceeded.

 Patients should remain under the care of a physician while using NORVIR. Patients should be advised to take NORVIR and other concomitant antiretroviral therapy every day as prescribed. NORVIR must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of NORVIR 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.

 NORVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using NORVIR.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**

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- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if NORVIR can be passed to the baby through breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

 Sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death.

Drug Interactions

 NORVIR 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.

 If they are receiving estrogen-based hormonal contraceptives, additional or alternate contraceptive measures should be used during therapy with NORVIR.

Potential Adverse Effects

 Pre-existing liver disease including Hepatitis B or C can worsen with use of NORVIR. This can be seen as worsening of transaminase elevations or hepatic decompensation. Patients should be advised that their liver function tests will need to be monitored closely especially during the first several months of NORVIR treatment and that they should notify their healthcare provider if they develop the signs and symptoms of worsening liver disease including loss of appetite, abdominal pain, jaundice, and itchy skin.

 Pancreatitis, including some fatalities, has been observed in patients receiving NORVIR therapy. Your patients should let you know of signs and symptoms (nausea, vomiting, and abdominal pain) that might be suggestive of pancreatitis.

 Skin rashes ranging in severity from mild to Stevens-Johnson syndrome have been reported in patients receiving NORVIR. Patients should be advised to contact their healthcare provider if they develop a rash while taking NORVIR. The healthcare provider will determine if treatment should be continued or an alternative antiretroviral regimen used.

 NORVIR may produce changes in the electrocardiogram (e.g., PR prolongation). Patients should consult their physician if they experience symptoms such as dizziness, lightheadedness, abnormal heart rhythm or loss of consciousness.

 Treatment with NORVIR therapy can result in substantial increases in the concentration of total cholesterol and triglycerides.

 New onset of diabetes or exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported. Patients should be advised to notify their healthcare provider if they develop the signs and symptoms of diabetes mellitus including frequent urination, excessive thirst, extreme hunger or unusual weight loss and/or an increased blood sugar while on NORVIR as they may require a change in their diabetes treatment or new treatment.

 Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including NORVIR.

 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.

 Patients with hemophilia may experience increased bleeding when treated with protease inhibitors such as NORVIR.

 If they are receiving sildenafil, tadalafil, or vardenafil, they may be at an increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor. They should seek medical assistance immediately if they develop a sustained penile erection lasting more than 4 hours while taking NORVIR and a PDE 5 Inhibitor such as Viagra®, Cialis® or Levitra®. Concomitant use of Revatio® (sildenafil) with NORVIR is contraindicated in patients with pulmonary arterial hypertension (PAH).

 Continued NORVIR therapy at a dose of 600 mg twice daily following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.

NORVIR tablets and oral solution are manufactured by:

Abbott Laboratories

North Chicago, IL 60064 USA

Patient Information

NORVIR® (NOR-VEER)

(ritonavir)

Tablet

NORVIR® (NOR-VEER)

(ritonavir)

Oral Solution

Reference ID: 3089891

Read this Patient Information before you start taking NORVIR and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

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 is a prescription anti-HIV medicine used with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. NORVIR is a type of anti-HIV medicine called a protease inhibitor. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

When used with other HIV medicines, NORVIR may reduce the amount of HIV in your blood (called "viral load"). NORVIR may also help to increase the number of CD_4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD_4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections). Patients who took NORVIR in clinical studies had significant reductions in both death and AIDS defining diseases; however NORVIR may not have these effects in all patients.

NORVIR does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using NORVIR.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection**. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Who should not take NORVIR?

Do not take NORVIR if you 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.

Do not take NORVIR with any of the following medicines:

- alfuzosin (Uroxatral)

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- amiodarone (Cordarone, Nexterone, Pacerone), flecainide (Tambocor), propafenone (Rhythmol) or quinidine (Nuedext, Quinaglute, Cardioquin, Quinidex, and others)
- voriconazole (VFend) if Norvir dose is 400 mg every 12 hours or greater
- dihydroergotamine (D.H.E. 45, Embolex, Migranal), ergonovine, ergotamine (Cafergot, Ergomar) methylergonovine (Methergine)
- cisapride (Propulsid)
- St. John's Wort (Hypericum perforatum)
- the cholesterol lowering medicines lovastatin (Mevacor, Altoprev, Advicor) or simvastatin (Zocor, Simcor, Vytorin)
- pimozide (Orap)
- sildenafil (Revatio) only when used for the treatment of pulmonary arterial hypertension
- oral midazolam or triazolam (Halcion)

Serious problems can happen if you or your child takes any of these medicines with NORVIR.

What should I tell my doctor before taking NORVIR?

Before taking NORVIR, tell your doctor if you:

- have liver problems, including Hepatitis B or Hepatitis C.
- have heart problems.
- have high blood sugar (diabetes).
- have bleeding problems or hemophilia.
- are pregnant or plan to become pregnant. It is not known if NORVIR can harm your unborn baby. **Pregnancy Registry:** You and your doctor will need to decide if taking NORVIR is right for you. If you take NORVIR while you are pregnant, talk to your doctor about how you can take part in the Antiretroviral Pregnancy Registry. The purpose of the registry is to follow the health of you and your baby.
- are breastfeeding. **Do not breastfeed.** We do not know if NORVIR can be passed to the baby through your breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Taking NORVIR and certain other medicines may affect each other causing serious side effects. NORVIR may affect the way other medicines work and other medicines may affect how NORVIR works.

Especially tell your doctor if you take:

- medicine to treat HIV
- estrogen-based contraceptives (birth control). NORVIR might reduce the effectiveness of estrogen-based contraceptives. You must take additional precautions for birth control such as a condom.
- medicine for pain such as tramadol (Ryzolt, Ultracet, Conzip, Ultram), propoxyphene, or meperidine (Demerol)
- medicine to treat alcohol abuse such as disulfiram (Antabuse)
- medicine for your heart such as disopyramide (Norpace), lidocaine (Xylocaine Viscous), mexiletine, digoxin (Lanoxin), nifedipine (Procardia, Adalat, Afeditab CR), diltiazem (Cardizem, Dilacor, Cartia, Diltzac, Dilt, Taztia, Tiazac) or verapamil (Calan, Covera, Isoptin, Tarka, Verelan)
- medicines for panic disorder or anxiety such as buspirone, clorazepate, diazepam, estazolam, flurazepam, and zolpidem
- medicine for cancer such as dasatinib (Sprycel), nilotinib (Tasigna) vincristine, or vinblastine
- warfarin (Coumadin, Jantoven)
- medicine for seizures such as carbamazepine (Carbatrol, Equetro, Tegretol, Epitol), clonazepam (Klonopin), ethosuximide (Zarontin, Ethosuximide), divalproex (Depakote, Divalproex Sodium), lamotrigine (Lamictal) or phenytoin (Dilantin, Phenytek)
- medicine for depression such as nefazodone, bupropion (Wellbutrin, Aplenzin, Zyban), desipramine (Norpramin) or trazadone, fluoxetine (Prozac), paroxetine (Paxil), amitriptyline, or nortriptyline
- medicine for nausea and vomiting such as dronabinol (Marinol) or perphenazine
- medicine for fungal infections such as ketoconazole (Nizoral), itraconazole (Sporanox, Onmel) or voriconazole (VFend)
- colchicine (Colcrys, Col-Probenecid, Probenecid and Colchine)
- medicine for infections such as clarithromycin (Prevpac, Biaxin), rifabutin (Mycobutin), rifampin (Rimactane, Rifadin, Rifater, Rifamate), atovaquone (Mepron, Malarone), quinine (Qualaquin) or metronidazole (Flagyl, Helidac, Metrocream)
- medicine used to treat blood pressure, a heart attack, heart failure, or to lower pressure in the eye such as metoprolol (Lopressor, Toprol-XL), timolol (Cosopt, Betimol, Timoptic, Isatolol, Combigan)
- medicine for lung disease such as theophylline and salmeterol (Serevent)
- bosentan (Tracleer)
- medicine to prevent organ transplant failure such as cyclosporine (Gengraf, Sandimmune, Neoral), tacrolimus (Prograf,) sirolimus (Rapamune)
- steroids such as dexamethasone, fluticasone (Advair Diskus, Veramyst, Flovent, Flonase) or prednisone
- a narcotic medicine such as methadone (Methadose, Dolophine Hydrochloride) or fentanyl (Abstral, Actiq, Fentora, Lazanda, Onsolis, Duragesic)

- medicine to treat schizophrenia such as risperidone (Risperdal) or thioridazine
- medicine to treat erectile dysfunction or pulmonary hypertension such as sildenafil (Viagra, Revatio), vardenafil (Levitra, Staxyn), tadalafil (Cialis, Adcirca)
- midazolam by injection
- methamphetamine (Desoxyn)
- cholesterol lowering medicine such as atorvastatin (Lipitor) or rosuvasatin (Crestor)

This is not a complete list of medicines that you should tell your doctor that you are taking. Ask your doctor, provider or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine. Do not start any new medicines while you are taking NORVIR without first talking with your doctor.

How should I take NORVIR?

- Take NORVIR exactly as prescribed by your doctor.
- You should stay under a doctor's care when taking NORVIR. Do not change your dose of NORVIR or stop your treatment without talking with your doctor first.
- If your child is taking NORVIR, your child's doctor will decide the right dose based on your child's height and weight. Tell your doctor if your child's weight changes. Your child should take NORVIR with food. If your child does not tolerate NORVIR Oral Solution, ask your child's doctor for advice.
- Swallow NORVIR tablets whole. Do not chew, break, or crush tablets before swallowing. If you cannot swallow NORVIR tablets whole, tell your doctor. You may need a different medicine.
- Take NORVIR with meals.
- NORVIR Oral Solution is peppermint or caramel flavored. You can take it alone, or may improve the taste by mixing it with 8 ounces of chocolate milk, Ensure®, or Advera®. NORVIR Oral Solution should be taken within 1 hour if mixed with these fluids. Ask your doctor, nurse or pharmacist about other ways to improve the taste of NORVIR Oral Solution.
- Do not run out of NORVIR. Get your NORVIR prescription refilled from you doctor or pharmacy before you run out.
- If you miss a dose of NORVIR, 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 NORVIR, call your local poison control center or go to the nearest hospital emergency room right away.

What are the possible side effects of NORVIR?

Reference ID: 3089891

NORVIR can cause serious side effects including:

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

Reference ID: 3089891

- lightheadedness
- feel faint or pass out
- abnormal heart beat

- **Increase in cholesterol and triglyceride levels.** Treatment with NORVIR may increase your blood levels of cholesterol and triglycerides. Your doctor should do blood test before you start your treatment with NORVIR 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 NORVIR can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your doctor if you notice an increase in thirst or urinate often while taking NORVIR.
- **Changes in your immune system (Immune reconstitution syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your doctor right away if you start having new symptoms after starting your HIV medicine.
- **Change in body fat**. These changes can happen in people who take antiretroviral therapy. The changes may include an increase amount of fat in the upper back and neck ("buffalo hump"), breast, and around the backand stomach area. 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 NORVIR.

The most common side effects of NORVIR include:

- feeling weak or tired
- nausea
- vomiting
- diarrhea
- loss of appetite
- abdominal pain
- changes in taste
- tingling feeling or numbness in hands or feet or around the lips
- headache
- dizziness

NORVIR liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of NORVIR, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

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Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of NORVIR. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I Store NORVIR?

- Store NORVIR tablets and NORVIR Oral Solution at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not refrigerate NORVIR Oral Solution.
- Shake NORVIR Oral Solution well before each use.
- Keep NORVIR Oral Solution away from heat.
- Store NORVIR tablets and NORVIR oral solution in the original container given to you by the pharmacist.
- Exposure of NORVIR tablets to high humidity outside the original container for longer than 2 weeks is not recommended.
- Use NORVIR tablets and NORVIR Oral Solution by the expiration date on the bottle.

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

General information about NORVIR

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

This leaflet summarizes the most important information about NORVIR. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about NORVIR that is written for healthcare professionals.

For more information, call 1-800-633-9110.

What are the ingredients in NORVIR?

Active ingredient: ritonavir

Inactive ingredients:

NORVIR Tablet: copovidone, anhydrous dibasic calcium phosphate, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The film coating contains: hypromellose, titanium dioxide, polyethylene

glycol 400, hydroxypropyl cellulose, talc, polyethylene glycol 3350, colloidal silicon dioxide, and polysorbate 80.

NORVIR Oral Solution: ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C Yellow No. 6.

This Patient Information has been approved by the U.S. Food and Drug Administration.

NORVIR tablets and oral solution are manufactured by:

Abbott Laboratories

North Chicago, IL 60064 USA

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Rev. 12/2011

Reference ID: 3089891