

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-659 / S-034

20-945 / S-017

Trade Name: Norvir

Generic Name: (ritonavir)

Sponsor: Abbott Laboratories

Approval Date: October 6, 2005

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20-945 / S-017

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APPLICATION NUMBER:

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20-945 / S-017

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-659/S-034
NDA 20-945/S-017

Abbott Laboratories
Attn: Mary Ellen Snyder
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Dept RA76, Bldg, APO30-1NE
Abbott Park, IL 60064-6157

Dear Ms Snyder:

Please refer to your supplemental new drug application 20-659 (034) and 20-945 (017) dated April 6, 2005 received on April 7, 2005 submitted under section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act for NORVIR (ritonavir) oral solution and soft gelatin capsules.

These supplemental new drug applications provide for the use of NORVIR (ritonavir) oral solution in combination with other antiretroviral agents for the treatment of HIV-infection in pediatric patients from one month _____

We completed our review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and text for the patient package insert.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-659/S-034 & 20-945/S-017**". Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to

NDA 20-659/S-034

NDA 20-945/017

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the Division of Antiviral Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Vasavi Reddy, RPh, Regulatory Project Manager, at (301) 796-0793.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Center for Drug Evaluation & Research
Food & Drug Administration

Enclosure (label)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeffrey Murray
10/6/2005 09:28:09 AM

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APPLICATION NUMBER:

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APPROVED LABELING



Norvir®
(Nos. 1940 and 6633)
NEW

DN1039V4 CR 25-00005144
October 3, 2005
Page 1 of 48

NORVIR®

(ritonavir capsules) Soft Gelatin
(ritonavir oral solution)

Rx only

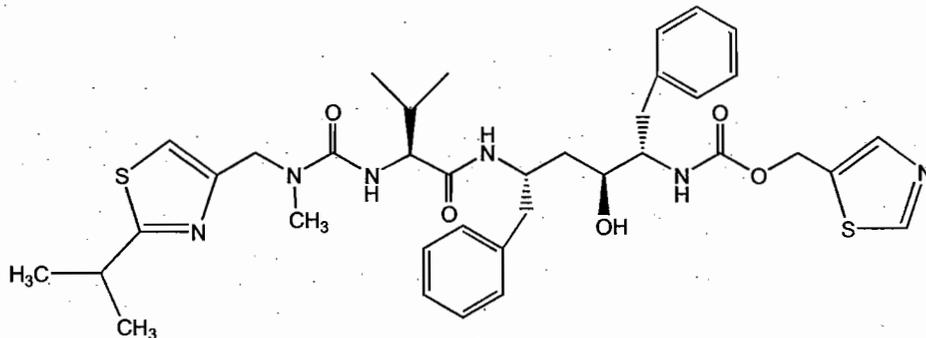
WARNING

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

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 $C_{37}H_{48}N_6O_5S_2$, 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 soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: Butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.

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.

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. 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 Vitro*

The activity of ritonavir was assessed *in vitro* in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC₅₀) of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC₅₀ for low passage clinical isolates was 22 nM (n = 13). In MT₄ cells, ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Studies which measured cytotoxicity of ritonavir on several cell lines showed that > 20 μM was required to inhibit cellular growth by 50% resulting in an *in vitro* therapeutic index of at least 1000.

Resistance

HIV-1 isolates with reduced susceptibility to ritonavir have been selected *in vitro*. Genotypic analysis of these isolates showed mutations in the HIV protease gene at amino



acid positions 84 (Ile to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic (n = 18) and genotypic (n = 44) changes in HIV isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Mutations associated with the HIV viral protease in isolates obtained from 41 patients appeared to occur in a stepwise and ordered fashion; in sequence, these mutations were position 82 (Val to Ala/Phe), 54 (Ile to Val), 71 (Ala to Val/Thr), and 36 (Ile to Leu), followed by combinations of mutations at an additional 5 specific amino acid positions. Of 18 patients for which both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir *in vitro*. All 18 patients possessed one or more mutations in the viral protease gene. The 82 mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a ≥ 5 -fold decrease in viral sensitivity *in vitro* from baseline. The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established.

Cross-Resistance to Other Antiretrovirals

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 2 patients had a decrease in susceptibility to nelfinavir (12- 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 isolate tested *in vitro* retained full susceptibility to ritonavir.



Pharmacokinetics

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients ($CD_4 \geq 50$ cells/ μ L). See Table 1 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.

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. After a single 600 mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule ($n = 57$) and oral solution ($n = 18$) formulations yielded mean \pm SD areas under the plasma concentration-time curve (AUCs) of 121.7 ± 53.8 and 129.0 ± 39.3 μ g·h/mL, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 KCal; 14.5% fat, 9% protein, and 76% carbohydrate).

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

Table 1. 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.

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/m² twice-daily to 400 mg/m² twice-daily in PACTG Study 340, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m² twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m²) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m² twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m² twice daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m² twice-daily compared to the 350 mg/m² 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/m² twice-daily in children < 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

Renal Insufficiency

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

Hepatic Insufficiency

Dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic insufficiency (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-Drug Interactions

See also **CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS - Drug Interactions.**

Table 2 and Table 3 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 **PRECAUTIONS - Drug Interactions.**

Table 2. Drug Interactions - Pharmacokinetic Parameters for Ritonavir in the Presence of the Co-administered Drug (See PRECAUTIONS - Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of NORVIR (mg)	n	AUC % (95% CI)	C_{max} (95% CI)
Clarithromycin	500 q12h, 4 d	200 q8h, 4 d	22	↑ 12% (2, 23%)	↑ 15% (2, 28%)
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%)
Fluoxetine	30 q12h, 8 d	600 single dose, 1 d	16	↑ 19% (7, 34%)	↔
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 18% (-3, 52%)	↑ 10% (-11, 36%)
Rifampin	600 or 300 daily, 10 d	500 q12h, 20 d	7, 9*	↓ 35% (7, 55%)	↓ 25% (-5, 46%)
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	10	↔	↔



Table 3. Drug Interactions - Pharmacokinetic Parameters for Co-administered Drug in the Presence of NORVIR (See PRECAUTIONS - Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of NORVIR (mg)	n	AUC % (95% CI)	C _{max} (95% CI)
Alprazolam	1, single dose	500 q12h, 10 d	12	↓ 12% (-5,30%)	↓ 16% (5, 27%)
Clarithromycin	500 q12h, 4 d	200 q8h, 4 d	22	↑ 77% (56, 103%)	↑ 31% (15, 51%)
14-OH clarithromycin metabolite				↓ 100%	↓ 99%
Desipramine	100, single dose	500 q12h, 12 d	14	↑ 145% (103, 211%)	↑ 22% (12, 35%)
2-OH desipramine metabolite				↓ 15% (3, 26%)	↓ 67% (62, 72%)
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%)
Fluticasone propionate aqueous nasal spray	200 mcg qd, 7 d	100 mg q12h, 7 d	18	↑ approximately 350-fold ⁶	↑ approximately 25-fold ⁶
Indinavir ¹	400 q12h, 15 d	400 q12h, 15 d	10	↑ 6% (-14, 29%) ↓ 7% (-25, 16%)	↓ 51% (40, 61%) ↓ 62% (52, 70%)
Ketoconazole	200 daily, 7 d	500 q12h, 10 d	12	↑ 3.4-fold (2.8, 4.3X)	↑ 55% (40, 72%)
Meperidine	50 oral single dose	500 q12h, 10 d	8	↓ 62% (59, 65%)	↓ 59% (42, 72%)
Normeperidine metabolite			6	↑ 47% (-24, 345%)	↑ 87% (42, 147%)
Methadone ²	5, single dose	500 q12h, 15 d	11	↓ 36% (16, 52%)	↓ 38% (28, 46%)
Rifabutin	150 daily, 16 d	500 q12h, 10 d	5, 11*	↑ 4-fold (2.8, 6.1X)	↑ 2.5-fold (1.9, 3.4X)
25-O-desacetyl rifabutin metabolite				↑ 35-fold (25, 78X)	↑ 16-fold (14, 20X)
Saquinavir ³	400 BID steady-state	400 BID steady-state	7	↑ 17-fold (9, 31X)	↑ 14-fold (7, 28X)
Sildenafil	100, single dose	500 BID, 8 d	28	↑ 11-fold	↑ 4-fold
Sulfamethoxazole ⁴	800, single dose	500 q12h, 12 d	15	↓ 20% (16, 23%)	↔
Theophylline	3 mg/kg q8h, 15 d	500 q12h, 10 d	13, 11*	↓ 43% (42, 45%)	↓ 32% (29, 34%)
Trazodone	50 mg, single dose	200 mg q12h, 4 doses	10	↑ 2.4-fold	↑ 34%
Trimethoprim ⁴	160, single dose	500 q12h, 12 d	15	↑ 20% (3, 43%)	↔
Warfarin	5, single dose	400 q12h, 12d	12	↑ 9% (-17, 44%) ⁵ ↓ 33% (-38, -27%) ⁵	↓ 9% (-16, -2%) ⁵ ↔
S-Warfarin					
R-Warfarin					
Zidovudine	200 q8h, 4 d	300 q6h, 4 d	9	↓ 25% (15, 34%)	↓ 27% (4, 45%)



- 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 Comparison to a standard saquinavir HGC 600 mg t.i.d. regimen (n = 114). Saquinavir C_{\min} was $0.48 \pm 0.36 \mu\text{g/mL}$ for 400/400 mg BID compared to below quantifiable limits for Saquinavir HGC 600 mg TID.
 - 4 Sulfamethoxazole and trimethoprim taken as single combination tablet.
 - 5 90% CI presented for R- and S-warfarin AUC and C_{\max} ratios.
 - 6 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.

INDICATIONS AND USAGE

NORVIR is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on the results from a study in patients with advanced HIV disease that showed a reduction in both mortality and AIDS-defining clinical events for patients who received NORVIR either alone or in combination with nucleoside analogues. Median duration of follow-up in this study was 13.5 months.

Description of 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.

Advanced Patients with Prior Antiretroviral Therapy

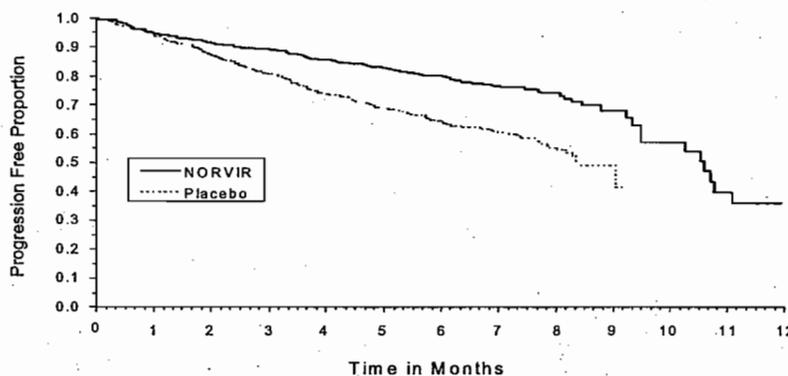
Study 247 was a randomized, double-blind trial (with open-label follow-up) conducted in HIV-infected patients with at least nine months of prior antiretroviral therapy and baseline CD_4 cell counts $\leq 100 \text{ cells}/\mu\text{L}$. NORVIR 600 mg twice-daily or placebo was added to each patient's 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 $\text{cells}/\mu\text{L}$. 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



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 Treatment Regimen in Study 247

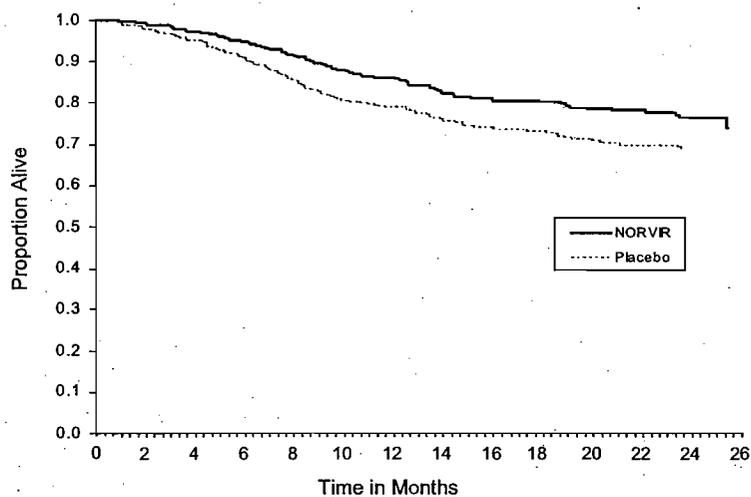


Figure 3 and Figure 4 summarize the mean change from baseline for CD₄ cell count and plasma HIV RNA (copies/mL), respectively, during the first 24 weeks for the double-blind phase of Study 247.



Figure 3. Mean Change from Baseline in CD₄ Cell Count (cells/ μ L) During the Double-blind Phase of Study 247

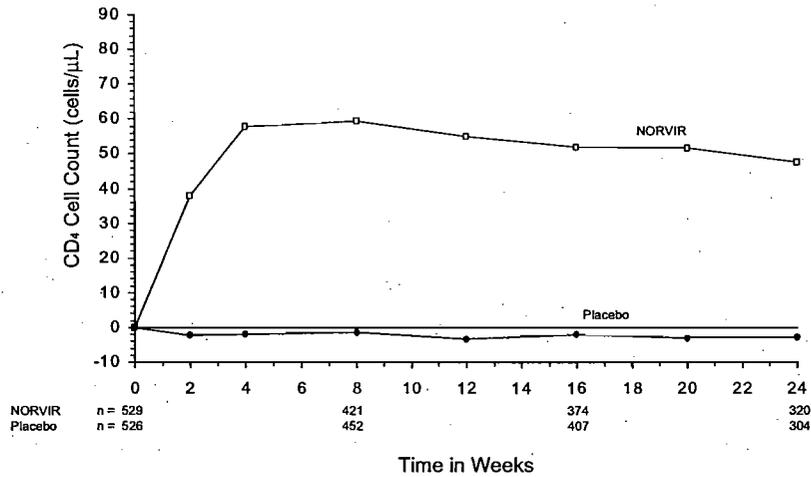
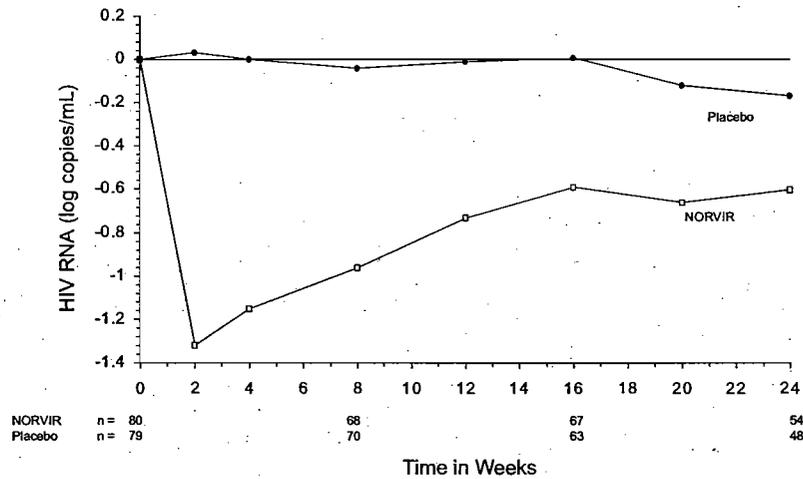


Figure 4. Mean Change from Baseline in HIV RNA (log copies/mL) During the Double-blind Phase of Study 247





Patients Without Prior Antiretroviral Therapy

In Study 245, 356 antiretroviral-naïve HIV-infected patients (mean baseline $CD_4 = 364$ cells/ μ L) 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/ μ L) During Study 245

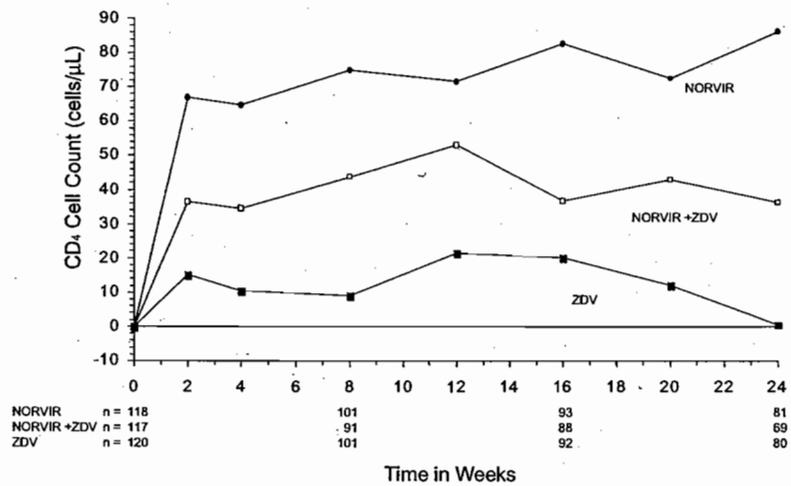
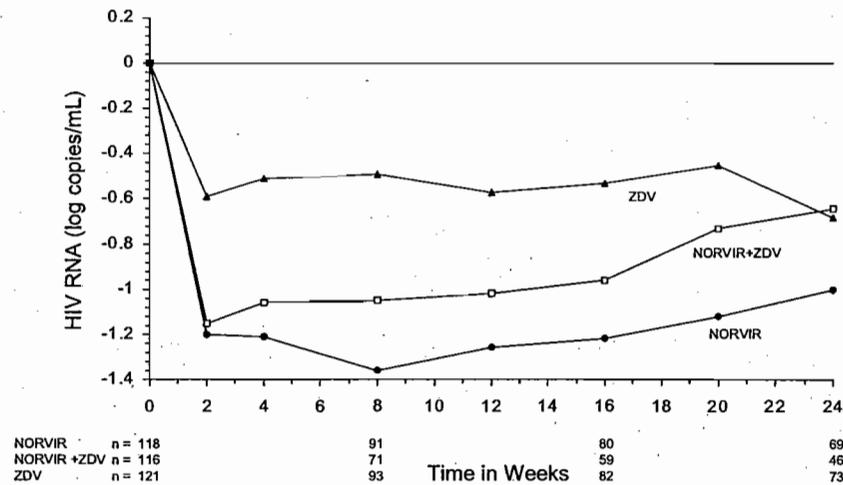




Figure 6. Mean Change from Baseline in HIV RNA (log copies/mL) During Study 245



CONTRAINDICATIONS

NORVIR is contraindicated in patients with known hypersensitivity to ritonavir or any of its ingredients.

Co-administration of NORVIR is contraindicated with the drugs listed in Table 4 (also see **PRECAUTIONS -Table 5. Drugs that Should Not be Co-administered with NORVIR**) because competition for primarily CYP3A by ritonavir could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression.



Table 4. Drugs that are Contraindicated with NORVIR

Drug Class	Drugs Within Class That Are CONTRAINDICATED With NORVIR
Alpha ₁ -adrenoreceptor antagonist	Alfuzosin HCL
Antiarrhythmics	amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	astemizole, terfenadine
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI Motility Agent	cisapride
Neuroleptic	pimozide
Sedative/hypnotics	midazolam, triazolam

WARNINGS

ALERT: Find out about medicines that should NOT be taken with NORVIR. This statement is included on the product's bottle label.

Drug Interactions

Ritonavir is an inhibitor of cytochrome P450 3A (CYP3A) both *in vitro* and *in vivo*. Ritonavir also inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A.

Co-administration of ritonavir and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of other drugs that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics - Drug-Drug Interactions**, **CONTRAINDICATIONS - Table 4. Drugs that are Contraindicated with NORVIR**, **PRECAUTIONS - Table 5. Drugs that Should Not be Co-administered with NORVIR**, **Table 6. Established Drug Interactions** and **Table 7 and Table 8. Predicted Drug Interactions: Use With Caution**).

The magnitude of the interactions and therapeutic consequences between ritonavir and the drugs listed in **Table 7 and Table 8. Predicted Drug Interactions: Use With Caution** cannot be predicted with any certainty. When co-administering ritonavir with any agent listed in **Table 7 and Table 8. Predicted Drug Interactions: Use With Caution**, special attention is warranted. Refer to **PRECAUTIONS - Established Drug Interactions and Predicted Drug Interactions** for additional information.



Cardiac and neurologic events have been reported with ritonavir when co-administered with disopyramide, mexiletine, nefazodone, fluoxetine and beta blockers. The possibility of drug interaction cannot be excluded.

Particular caution should be used when prescribing sildenafil in patients receiving NORVIR. Co-administration of NORVIR with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection (see **PRECAUTIONS - Drug Interactions, Table 6.**

Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies and the complete prescribing information for sildenafil).

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

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

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, 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 (see **PRECAUTIONS - Drug Interactions**).

Allergic Reactions

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

Hepatic Reactions

Hepatic 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 10). 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.

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

Pancreatitis

Pancreatitis has been observed in patients receiving 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.

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.

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.

PRECAUTIONS

General

Ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function (see **WARNINGS** and **CLINICAL PHARMACOLOGY - Hepatic Insufficiency**).

Resistance/Cross-resistance

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

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the



reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, 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.

Lipid Disorders

Treatment with NORVIR therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating NORVIR therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS - Table 5 and Table 7** for additional information on potential drug interactions with NORVIR and HMG CoA reductase inhibitors.

Information For Patients

A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with NORVIR.** A Patient Package Insert (PPI) for Norvir is available for patient information.

Patients should be informed that NORVIR is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that the long-term effects of NORVIR are unknown at this time. They should be informed that NORVIR therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take NORVIR with food, if possible.



Patients should be informed to take NORVIR every day as prescribed. Patients should not alter the dose or discontinue NORVIR without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

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.

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.

Drug Interactions

Ritonavir has been found to be an inhibitor of cytochrome P450 3A (CYP3A) both *in vitro* and *in vivo* (Table 3). 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. 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 as well as other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9.



Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed both in **CONTRAINDICATIONS - Table 4** and under **Drugs That Should Not Be Co-administered with NORVIR in Table 5**.

Those drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in **CLINICAL PHARMACOLOGY - Table 2** and **Table 3**. The clinical recommendations based on the results of these studies are listed in **Table 6. Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies**. A systematic review of over 200 medications prescribed to HIV-infected patients was performed to identify potential drug interactions with ritonavir.² There are a number of agents in which CYP3A or CYP2D6 partially contribute to the metabolism of the agent. In these cases, the magnitude of the interaction and therapeutic consequences cannot be predicted with any certainty.

When co-administering ritonavir with calcium channel blockers, immunosuppressants, some HMG-CoA reductase inhibitors (see **WARNINGS - Drug Interactions**), some steroids, or other substrates of CYP3A, or most antidepressants, certain antiarrhythmics, and some narcotic analgesics which are partially mediated by CYP2D6 metabolism, it is possible that substantial increases in concentrations of these other agents may occur, possibly requiring a dosage reduction (> 50%); examples are listed in **Table 7. Predicted Drug Interactions: Use With Caution, Dose Decrease May Be Needed**.

When co-administering ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted. With some agents, the metabolism may be induced, resulting in decreased concentrations (see **Table 8. Predicted Drug Interactions: Use With Caution, Dose Increase May Be Needed**).



Table 5. Drugs that Should Not be Co-administered with NORVIR

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (<i>hypericum perforatum</i>)	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 serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.



Table 6. Established Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies (see CLINICAL PHARMACOLOGY - Table 2 and Table 3 for Magnitude of Interaction)

Concomitant Drug Class: Drug Name	Effect on Concentration of Ritonavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
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 saquinavir and ritonavir ↑ saquinavir (↑ AUC, ↑ C _{max} , ↑ C _{min})	When used in combination therapy for up to 24 weeks, doses of 400 mg b.i.d. of ritonavir and saquinavir were better tolerated than the higher doses of the combination. Saquinavir plasma concentrations achieved with Invirase® (saquinavir mesylate) (400 mg BID) and ritonavir (400 mg BID) are similar to those achieved with Fortovase™ (saquinavir) (400 mg BID) and ritonavir (400 mg BID)
Nucleoside Reverse Transcriptase Inhibitor: didanosine		Dosing of didanosine and ritonavir should be separated by 2.5 hours to avoid formulation incompatibility
<i>Other Agents</i>		
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)
Anticoagulant: warfarin	↓ R-warfarin ↑ S-warfarin	Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated.
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.
Antifungal: ketoconazole	↑ ketoconazole	High doses of ketoconazole (> 200 mg/day) are not recommended
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment the following dosage adjustments should be considered: <ul style="list-style-type: none">• 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)
Bronchodilator: theophylline	↓ theophylline	Increased dosage of theophylline may be required; therapeutic monitoring should be considered
Erectile Dysfunction: sildenafil	↑ sildenafil	Sildenafil should not exceed a maximum single dose of 25 mg in a 48-hour period in patients receiving concomitant ritonavir therapy (see WARNINGS)
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 (see WARNINGS).
Narcotic Analgesic: methadone	↓ methadone	Dosage increase of methadone may be considered
Oral Contraceptive: ethinyl estradiol	↓ ethinyl estradiol	Dosage increase or alternate contraceptive measures should be considered



Table 7. Predicted Drug Interactions: Use with Caution, Dose Decrease of Co-administered Drug May Be Needed (see WARNINGS)

Examples of Drugs in Which Plasma Concentrations May Be Increased By Co-Administration With NORVIR	
Drug Class	Examples of Drugs
Analgesics, narcotic	tramadol, propoxyphene
Antiarrhythmics	disopyramide, lidocaine, mexilitine
Anticonvulsants	carbamazepine, clonazepam, ethosuximide
Antidepressants	bupropion, nefazodone, selective serotonin reuptake inhibitors (SSRIs), tricyclics
Antiemetics	dronabinol
Antifungals	itraconazole
Antiparasitics	quinine
β-blockers	metoprolol, timolol
Calcium channel blockers	diltiazem, nifedipine, verapamil
Hypolipidemics, HMG CoA reductase inhibitors ¹	atorvastatin ²
Immunosuppressants	cyclosporine, tacrolimus, sirolimus (rapamycin)
Neuroleptics	perphenazine, risperidone, thioridazine
Sedative/hypnotics	clorazepate, diazepam, estazolam, flurazepam, zolpidem
Steroids	dexamethasone, fluticasone, prednisone
Stimulants	methamphetamine

- 1 Co-administration with lovastatin and simvastatin is not recommended (see **WARNINGS - Drug Interactions**).
- 2 Use lowest possible dose of atorvastatin with careful monitoring or consider HMG-CoA reductase inhibitor such as pravastatin or fluvastatin.

Table 8. Predicted Drug Interactions: Use with Caution, Dose Increase of Co-administered Drug May Be Needed (see WARNINGS)

Examples of Drugs in Which Plasma Concentrations May Be Decreased By Co-Administration With NORVIR	
Anticonvulsants	phenytoin, divalproex, lamotrigine
Antiparasitics	atovaquone



Carcinogenesis and Mutagenesis

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 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.

Pregnancy, Fertility, and Reproduction

Pregnancy Category B

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.

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.

There are, however, 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.

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.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether zidovudine 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 breast-feed if they are receiving NORVIR.**

Pediatric Use

In HIV-infected patients age > 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.

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.



ADVERSE REACTIONS

Adults

The safety of NORVIR alone and in combination with nucleoside reverse transcriptase inhibitors was studied in 1270 adult patients. Table 9 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 ongoing study 462. In that study, 141 protease inhibitor-naive, HIV-infected patients with mean baseline CD₄ 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 9. Percentage of Patients with Treatment-emergent Adverse Events¹ 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
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 ongoing 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.

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.



Post-Marketing Experience

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

Body as a Whole

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

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

Redistribution/accumulation of body fat has been reported (see **PRECAUTIONS - Fat Redistribution**).

Cardiovascular System

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.

Hemic and Lymphatic System

There have been reports of increased bleeding in patients with hemophilia A or B (see **PRECAUTIONS - Hemophilia**).



Nervous System

There have been postmarketing reports of seizure. Also, see Cardiovascular System.

Laboratory Abnormalities

Table 10 shows the percentage of adult patients who developed marked laboratory abnormalities.

Table 10. Percentage of Adult Patients, by Study and Treatment Group, with Chemistry and Hematology Abnormalities Occurring in > 3% of Patients Receiving NORVIR

Variable	Limit	Study 245 Naive Patients			Study 247 Advanced Patients		Study 462 PI-Naive Patients
		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

1 ULN = upper limit of the normal range.

- Indicates no events reported.



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 $\geq 2\%$ of pediatric patients enrolled in NORVIR clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in $\geq 3\%$ 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%).

OVERDOSAGE

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.

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.

DOSAGE AND ADMINISTRATION

NORVIR is administered orally. It is recommended that NORVIR be taken with meals if possible. Patients may improve the taste of NORVIR oral solution by mixing with chocolate milk, Ensure®, or Advera® within one hour of dosing. The effects of antacids on the absorption of ritonavir have not been studied.

Adults

Recommended Dosage

The recommended dosage of ritonavir is 600 mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily.

Concomitant Therapy

If saquinavir and ritonavir are used in combination, the dosage of saquinavir should be reduced to 400 mg twice daily. The optimum dosage of NORVIR (400 mg or 600 mg twice daily), in combination with saquinavir, has not been determined; however, the combination regimen was better tolerated in patients who received NORVIR 400 mg twice daily.



Pediatric Patients

Ritonavir should be used in combination with other antiretroviral agents (see **General Dosing Guidelines**). The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m² twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. If patients do not tolerate 400 mg/m² 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.

Pediatric Dosage Guidelines¹

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 can be calculated with the following equation:

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

General Dosing Guidelines

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



HOW SUPPLIED

NORVIR (ritonavir capsules) soft gelatin are white capsules imprinted with the corporate logo , 100 and the Abbo-Code DS, available in the following package size:

Bottles of 120 capsules each.....(NDC 0074-6633-22).

Bottles of 30 capsules each.....(NDC 0074-6633-30).

Recommended Storage

Store soft gelatin capsules in the refrigerator between 36-46°F (2-8°C) until dispensed. Refrigeration of NORVIR soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 77°F (25°C). Protect from light. Avoid exposure to excessive heat.

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) in the following size:

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

Recommended Storage

Store NORVIR oral solution at room temperature 68°F to 77°F (20°C to 25°C). 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.

REFERENCES

1. Sewester CS. Calculations. In: Drug Facts and Comparisons. St. Louis, MO: J.B. Lippincott Co; January, 1997:xix.
2. Bertz RJ and Granneman GR. Use of *in vitro* and *in vivo* data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet* 1997; 32(3):210-258.

 Norvir®
(Nos. 1940 and 6633)
NEW

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NORVIR®
(ritonavir capsules) Soft Gelatin
(ritonavir oral solution)

ALERT: Find out about medicines that should NOT be taken with NORVIR.

Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH NORVIR."

PATIENT INFORMATION
NORVIR® (NOR - VEER)

Generic name: ritonavir (rit-ON-uh-veer)

Please read this leaflet carefully before you start taking NORVIR. Also, read it each time you get your NORVIR prescription refilled, just in case something has changed.

Remember that this information does not take the place of careful discussions with your doctor when you start this medication and at check ups.

You should remain under a doctor's care when taking NORVIR and you should not change or stop treatment without first talking with your doctor.

You should tell your doctor about any medicine you are taking or planning to take because taking NORVIR with some medications can result in serious or life-threatening problems.

Talk to your doctor if you have any questions about NORVIR. Your doctor or pharmacist can also give you more information about NORVIR.

What is NORVIR and How Does it work?

NORVIR is in a class of medicines called the HIV protease (PRO-tee-ase) inhibitors. NORVIR is used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. NORVIR is for adults and for children age > 1 month and older.



HIV infection leads to the destruction of CD₄ (T) cells, which are important to the immune system. After a large number of CD₄ (T) cells have been destroyed, acquired immune deficiency syndrome (AIDS) develops.

NORVIR blocks HIV protease, a chemical which is needed for HIV to multiply. NORVIR reduces the amount of HIV and helps to increase the number of CD₄ (T) cells in your blood. 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.

Does NORVIR Cure HIV or AIDS?

NORVIR does not cure HIV infection or AIDS. The long-term effects of NORVIR are not known at this time. People taking NORVIR may still get opportunistic infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does NORVIR Reduce the Risk of Passing HIV to Others?

NORVIR does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How Should I Take NORVIR?

- You should stay under a doctor's care when taking NORVIR. Do not change your treatment or stop treatment without first talking with your doctor.
- It is very important that you take NORVIR every day exactly as your doctor prescribed it.
- The usual dose for adults is six 100 mg capsules or 7.5 mL of the oral solution twice a day (morning and night), in combination with other anti-HIV medicines.
- The dosing of NORVIR may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.



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- Children from > 1 month to 21 years of age can also take NORVIR. The child's doctor will decide the right dose based on the child's height and weight.
 - Take NORVIR with food if possible.
 - NORVIR Oral Solution is peppermint/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 items. Ask your doctor, nurse or pharmacist about other ways to improve the taste of NORVIR Oral Solution.
 - Do not change or stop taking NORVIR without first talking with your health care provider.
 - When your NORVIR supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to NORVIR and become harder to treat.
 - Be sure to set up a schedule and follow it carefully.
 - Only take medicine that has been prescribed specifically for you. Do not give NORVIR to others or take medicine prescribed for someone else.

What Should I Do if I Miss a Dose of NORVIR?

It is important that you do not miss any doses. 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.

What Happens If I Take Too Much NORVIR?

If you think that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

As with all prescription medicines, NORVIR should be kept out of the reach of young children. 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.

Who Should Not Take NORVIR?

Together with your doctor, you need to decide whether NORVIR is right for you.

- Do not take NORVIR if you are taking certain medicines. These could cause serious side effects that could cause death. Before you take NORVIR, you must tell your doctor about all the medicines you are taking or are planning to take. These include other prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with NORVIR, please read the section "MEDICINES YOU SHOULD NOT TAKE WITH NORVIR."

- Do not take NORVIR if you have had a serious allergic reaction to NORVIR or any of its ingredients.

Can I Take NORVIR With Other Medications?*

NORVIR may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or are planning to take.

MEDICINES YOU SHOULD NOT TAKE WITH NORVIR.

- *Do not take the following medicines with NORVIR because they can cause serious or life-threatening problems such as irregular heartbeat, breathing difficulties, or excessive sleepiness:*
 - Cordarone® (amiodarone)
 - Ergotamine, ergonovine, methylergonovine, and dihydroergotamine such as Cafegot®, Migranal®, D.H.E 45®, and others
 - Halcion® (triazolam)
 - Hismanal® (astemizole)
 - Orap® (pimozide)
 - Propulsid® (cisapride)



-
- Quinidine, also known as Quinaglute®, Cardioquin®, Quinidex®, and others
 - Rythmol® (propafenone)
 - Seldane® (terfenadine)
 - Tambocor® (flecainide)
 - Vascor® (bepridil)
 - Versed® (midazolam)
- Do not take NORVIR with St. John's wort (*hypericum perforatum*), an herbal product sold as a dietary supplement or products containing St. John's wort. Talk with your doctor if you are taking or are planning to take St. John's wort. Taking St. John's wort may decrease NORVIR levels and lead to increased viral load and possible resistance to NORVIR or cross-resistance to other antiretroviral medicines.
 - Do not take NORVIR with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between NORVIR and Lipitor® (atorvastatin); talk to your doctor before you take any of these cholesterol-lowering medicines with NORVIR.

Medicines That May Require Dosage Adjustments

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking NORVIR. Remember to tell your doctor all medicines you are taking or plan to take.

- The following medicines require dose reduction if taken with NORVIR:
 - If you are taking Viagra® (sildenafil), your doctor may lower your dose of Viagra.

Before you take Viagra with NORVIR, talk to your doctor about possible drug interactions and side effects. If you take Viagra and NORVIR together, you may be at risk of side effects of Viagra such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should get medical help immediately to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.



- If you are taking Oral contraceptives ("the pill") to prevent pregnancy, your doctor should increase the dose or you should use a different type of contraception since NORVIR may reduce the effectiveness of oral contraceptives.
- If you are taking Mycobutin® (rifabutin), your doctor will lower the dose of Mycobutin.
- **Other Special Considerations:**
NORVIR oral solution contains alcohol. Talk with your doctor if you are taking or planning to take metronidazole or disulfiram. Severe nausea and vomiting can occur.
- **If you are taking both didanosine (Videx) and NORVIR:**
Didanosine and NORVIR should be separated by at least 2.5 hours.
- Rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®, may reduce blood levels of NORVIR. Be sure to tell your doctor if you are taking rifampin.
- If you are taking or before you begin using inhaled Flonase® (fluticasone propionate), talk to your doctor about problems these two medicines may cause when taken together. Your doctor may choose not to keep you on inhaled Flonase®.

What Are the Possible Side Effects of NORVIR?

- This list of side effects is **not** complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.
- The most commonly reported side effects are: feeling weak/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, and dizziness.
- Blood tests in patients taking NORVIR may show possible liver problems. People with liver disease such as Hepatitis B and Hepatitis C who take NORVIR may have worsening liver disease. Liver problems including rare cases of death have occurred in patients taking NORVIR. It is unclear if NORVIR caused these liver problems because some patients had other illnesses or were taking other medicines.
- Some patients taking NORVIR can develop serious problems with their pancreas (pancreatitis) which may cause death. Tell your doctor if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.



- Some patients have large increases in triglycerides and cholesterol. The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.
- Diabetes and high blood sugar (hyperglycemia) have occurred in patients taking protease inhibitors. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medication. Others needed new diabetes medication.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- Allergic reactions ranging from mild to severe have occurred in patients taking NORVIR.

There have been other side effects noted in patients receiving NORVIR; however, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or persistent symptoms to your doctor immediately.

What Should I Tell My Doctor Before Taking NORVIR?

- *If you are pregnant or planning to become pregnant:* The effects of NORVIR on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking NORVIR. You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV, there is a chance that HIV can be transmitted through breast-feeding.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking NORVIR.



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- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Be sure to tell your doctor if you have diabetes or an increase in thirst and/or frequent urination.
 - *If you have hemophilia:* Some people with hemophilia have had increased bleeding. It is not known whether the protease inhibitors caused these problems. Be sure to tell your doctor if you have hemophilia types A and B.

How Do I Store NORVIR?

- Keep NORVIR and all other medicines out of the reach of children.
- Store NORVIR Oral Solution at room temperature. Do not refrigerate NORVIR Oral Solution. Avoid exposing NORVIR Oral Solution to excessive heat or cold.
- Refrigeration of NORVIR soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 77°F (25°C). Avoid exposing NORVIR soft gelatin capsules to excessive heat or cold.
- Store NORVIR soft gelatin capsules and NORVIR Oral Solution in the original container.
- Shake NORVIR Oral Solution well before each use.
- Use NORVIR soft gelatin capsules and NORVIR Oral Solution by the expiration date on the bottle.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

General Advice About Prescription Medicines

Talk to your doctor or other health care provider if you have any questions or concerns about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.



Norvir®
(Nos. 1940 and 6633)
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DN1039V4 CR 25-00005144
October 3, 2005
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-659 / S-034

20-945 / S-017

MEDICAL REVIEW

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 27, 2005

FROM: Kimberly A. Struble, PharmD
Division of Antiviral Products

TO: Division File

SUBJECT: Team Leader Memo for sNDA 20659 (SE5) for the use of Norvir (ritonavir) in HIV-1 infected pediatric patients greater than one month to two years of age

BACKGROUND:

Ritonavir is a member of the class of antiretrovirals known as protease inhibitors. Ritonavir was the first protease inhibitor to demonstrate a reduction in both mortality and CDC Class C AIDS-defining events. Ritonavir 100 mg capsules and oral solution received approval on March 1, 1996, for the treatment of HIV infection in adults in combination with other antiretroviral agents. Subsequently in April 1997, ritonavir was the first protease inhibitor approved for use in pediatric patients older than two years of age. According to the HHS treatment guidelines, ritonavir 600 mg twice daily is no longer recommended for use as the sole protease inhibitor in a regimen due to the high incidence of gastrointestinal intolerance. Today, ritonavir is predominately used as a pharmacokinetic enhancer. Ritonavir is a potent inhibitor of CYP 3A4 and is used to increase drug exposures and prolong serum half-lives of other protease inhibitors and is mainly used at 100-400 mg per day in combination with other protease inhibitors.

A Pediatric Written Request was originally issued for ritonavir on April 19, 1999. At this time, age appropriate formulations, with the exception of nelfinavir, were not available for other protease inhibitors. Although ritonavir was no longer used at the recommended dose of 600 mg twice daily, pharmacokinetic and safety data were important especially for children less than two years of age given the limited available treatment options and dosing information in this population. Nevertheless, dosing information in children greater than one month ~~to two years of age~~ may be important in clinical practice today for children who are unable to receive other protease inhibitor based regimens.

This supplement contains pharmacokinetic, safety and activity data in HIV-1 infected pediatric patients from two studies conducted by the Pediatric AIDS Clinical Trial Group (PACTG). Appropriate updates to the package insert based on these data were included in the submission. Abbott Laboratories response to the Written Request was presented to the Pediatric Exclusivity Board and the terms of the request were determined to be fulfilled. Pediatric Exclusivity was granted on June 15, 2005.

SUMMARY OF STUDIES:

PACTG 345 is a phase I/II, dose-finding, open-label study designed to assess the safety, tolerance, pharmacokinetics, and activity of RTV (350 mg/m² and 450 mg/m² twice daily) alone and in combination with lamivudine (4 mg/kg q 12h) and zidovudine (160 mg/m² q 8h) in HIV-1 infected infants and children.

Overall, 50 HIV-infected children ages one month to two years of age were enrolled. Pharmacokinetic data are available for 41 of the 50 enrolled patients as follows.

1 month to < 3 months: 20 (pharmacokinetic data available from 18 patients)
3 months to < 6 months: 15 (pharmacokinetic data available from 10 patients)
6 months to < 2 years: 15 (pharmacokinetic data available from 13 patients)

The pharmacokinetic data from this study allowed for dosing recommendations in children greater than one month summary:

1. Ritonavir exposures in infants and children less than after 350 or 450 mg/m² twice daily dosing were similar to historical data in older children after 250 to 350 mg/m² twice daily dosing; with the exception that steady-state trough concentrations were lower in children less than two years of age.
2. A high variability in ritonavir exposures was observed.
3. Higher ritonavir exposures were not evident with 450 mg/m² twice daily dose compared to the 350 mg/m² twice daily dose.
4. Additionally, increasing the ritonavir dose beyond 400 mg /m² will not lead to increased RTV concentrations. As a result, dosing regimen for HIV-infected pediatric patients remains the same (350 to 400 mg/m² twice daily), for children greater than one month and greater than two years of age.

Regarding HIV RNA and CD4 cell counts, no statistically significant differences were observed between the two dose groups. At Week 48, 8/17 (47%) of patients in cohort I (350 mg/m² twice daily) experienced virologic failure (confirmed HIV RNA > 400 copies/mL at or after Week 16) or treatment discontinuation compared to 22/33 (67%) of patients in cohort II (450 mg/m² twice daily). The proportion of patients with virologic failure or treatment discontinuation was 53% (9/17) in cohort I compared to 70% (23/33) in cohort II. These results are consistent with long-term ritonavir treatment in combination with lamivudine and zidovudine in adults. Of note, the results are not surprising given children were eligible to enroll if they (1) received ≥ 12 weeks of monotherapy (excluding lamivudine or protease inhibitors), or (2) received combination zidovudine with either stavudine, didanosine or zalcitabine providing their HIV RNA was > 10,000 copies/mL. As a result, patients could have varying degrees of nRTI resistance at baseline; thus, patients may have received only one or two active antiretroviral agents in their regimen.

No new or unexpected safety findings were observed. The safety profile appears similar to that observed in adults.

PACTG 366 is a phase I/II, open-label, management algorithm for highly antiretroviral experienced HIV-infected children and adolescents between 6 months and 21 years of age with rapidly progressive or advanced HIV disease for whom current antiretroviral therapy was failing. Patients received RTV 350 mg/m² twice daily.

In this study, 164 received antiretroviral regimens containing ritonavir (350 mg/m² twice daily), of which 14 patients were less than two years of age. As a result Dr. Pikis's review focused on the review of data in children less than two years of age. The pharmacokinetic data show ritonavir exposures in children ≤ 2 years of age were lower than in older children receiving 350 mg/m² BID dose, and also were lower than those observed in the PACTG 345 study. Overall the safety and activity were consistent with previous studies in children and adults.

The package insert includes pooled safety data from 265 pediatric patients > 1 month to 21 years of age. The most commonly observed drug-related events of moderate to severe intensity were vomiting, diarrhea and skin reaction. In addition, the most commonly reported Grade 3 or 4 laboratory abnormalities were neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anemia (4%) and elevated AST (3%).

SUMMARY AND RECOMMENDATIONS

Data from the two PACTG studies contained in this supplement support the use of ritonavir in children greater than one month . The Clinical Pharmacology, Precautions: Pediatric Use subsection, Adverse Reactions and Dosage and Administration section of the package insert were updated to include new information as a result of this review.

I concur with the findings of Drs. Andreas Pikis and Derek Zhang and recommend approval of this application

Kimberly A Struble, PharmD
Acting Medical Team Leader
DAVP

Concurrence:
HFD-530/Deputy DivDir/Murray

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Struble
10/5/2005 01:28:58 PM
MEDICAL OFFICER

Jeffrey Murray
10/6/2005 09:09:46 AM
MEDICAL OFFICER

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-659 (oral solution) 20-945 (capsule)	Submission Date(s): 04-06-2005
Brand Name	Norvir
Generic Name	Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Abbott
Other NDA(s)	20-680 (original capsule, no longer marketed)
Relevant IND(s)	43-718
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Indication	Treatment of HIV-1 infection

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has concluded that the clinical pharmacology information submitted to this NDA supplement is adequate to support the claim for Pediatric Exclusivity for Norvir and to make the relevant labeling revisions. Based on the submitted pharmacokinetic data, it is acceptable to expand the pediatric age range from > 2 years of age to > 1 month of age. The dosing regimen for HIV-infected pediatric patients does not change (350 to 400 mg/m² BID).

1.2 Post Marking Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Application Contents

Two studies provide pharmacokinetic data in HIV infected patients <2 years old of age.

Study PACTG 345 is the main study to support the Pediatric Exclusivity claim. The ritonavir dose regimens studied were 350 and 450 mg/m² BID. The number of subjects with pharmacokinetic data in each age group are as follows:

CLINICAL REVIEW

Application Type 20-659; 20-945
Submission Number 034; 017
Submission Code SE5

Letter Date April 6, 2005
Stamp Date April 7, 2005
PDUFA Goal Date October 6, 2005

Reviewer Name Andreas Pikis, M.D.
Review Completion Date October 4, 2005

Established Name Ritonavir
Trade Name NORVIR
Therapeutic Class Antiretroviral; HIV protease inhibitor
Applicant Abbott Laboratories

Priority Designation P

Formulation 100 mg soft gelatin capsules
80 mg/mL oral solution

Dosing Regimen Adults: 600 mg twice daily
Pediatric patients: 350 to 400 mg/m² twice
daily and not to exceed 600 mg twice daily

Indication Treatment of HIV infection in combination
with other antiretroviral drugs

Intended Population Children > 1 month to

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The pharmacokinetic, safety, and activity data submitted in this supplemental NDA (sNDA), together with the previous demonstration of efficacy in adult patients, support the approval of ritonavir (RTV) for the treatment of HIV-1 infected pediatric patients > 1 month _____ age. The submitted data complete the applicant's presentation of their pediatric development program for RTV. The Pediatric Exclusivity Board members agreed with the Division and concluded Abbott provided an adequate response to the Written Request. As a result, Pediatric Exclusivity was granted on June 15, 2005.

The applicant submitted data from two clinical trials conducted by the Pediatric AIDS Clinical Trial Group (PACTG) in response to the final amended Pediatric Written Request to provide information on the multiple-dose pharmacokinetic, safety, and activity of RTV in combination with other antiretroviral agents in HIV-1 infected children > 1 month to _____. The original Pediatric Written Request was issued on April 19, 1999 and was last amended on November 4, 2004. Study PACTG 345 is the pivotal study to support Pediatric Exclusivity and use of RTV in patients > 1 month to _____. Study PACTG 366 provided supportive pharmacokinetic and safety data.

Overall, the pharmacokinetic, safety, and activity data submitted in this sNDA allow for a reasonable recommendation for dosing RTV in pediatric patients > 1 month to _____. Pharmacokinetic results from study PACTG 345 showed that higher RTV exposures were not evident with 450 mg/m² BID dose compared to 350 mg/m² BID dose. Moreover, study PACTG 345 showed that RTV exposures after 350 or 450 mg/m² BID dosing in infants and children less than two years of age were similar to that previously observed in older children after 250 to 350 mg/m² BID dosing with the exception that steady-state trough concentrations were somewhat lower in children <2 years. The 250 and 350 mg/m² BID dosing in older children resulted in 58% and 33% higher C_{trough,ss} values, respectively, compared to the C_{trough,ss} values after 350 or 450 mg/m² BID dosing in the younger children (< 2 years). Based on these data, a dose regimen up to 350 to 400 mg/m² BID is recommended for children > 1 month to _____.

The antiviral activity and the overall adverse event profile of RTV in children appear similar to that observed in adults.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific Risk Management Activities were requested from the applicant.

1.2.2 Required Phase 4 Commitments

There were no recommendations for additional phase 4 studies or risk management steps based on the review of this supplement.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

RTV is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. RTV selectively inhibits the virus-specific processing of viral Gag and Gag-POL polyproteins in HIV-1 infected cells, thus preventing the formation of mature infectious virions. The mechanism of action of RTV is similar to other protease inhibitors (PIs) used for the treatment of HIV-infection. Currently, the approved dose in adults is 600 mg twice daily in combination with other antiretroviral agents. The currently recommended dose in children > 2 years of age is as follows:

400 mg/m² twice daily by mouth and should not exceed 600 mg twice daily. RTV should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. If patients do not tolerate 400 mg/m² 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.

As previously stated, this sNDA provides data to support dosing in pediatric patients > 1 month

2.2 Currently Available Treatment for Indications

At present, 23 antiretroviral drugs are approved in the United States for the treatment of HIV infection in adult patients. Pediatric dosing recommendations are presented in the product labels of 12 of these drugs and pediatric dosing is not recommended in another two product labels because of dose constraints (the two fixed-dose combination products, Combivir and Trizivir). HIV PIs prevent cleavage of protein precursors essential for viral replication. The use of PIs, in combination with other antiretroviral drugs, has led to significant improvement and prolonged survival in HIV-infected patients. However, the development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains critical. Accurate dosing across all pediatric age groups remains an important issue in limiting the

emergence of resistance and the impact of adverse events which are not uncommon with these drugs. The initial pediatric dosing recommendation for RTV (1997) was for children older than two years of age. The current submission attempts to provide dosing recommendations for children between 1 month and _____

2.3 Other Relevant Background Information

RTV was the first protease inhibitor for which clinical benefit was demonstrated based on the reduction of death and CDC Class C AIDS defining events. RTV was approved on March 1, 1996, for the treatment of HIV infection in adults in combination with other antiretroviral medications. In April 1997, RTV was approved by FDA for use in children older than 2 years of age. In fact, RTV was the first PI approved by FDA for children. However, due to poor tolerability, RTV is infrequently used today for its antiviral effect in combination treatment regimens. RTV is mainly used in lower doses to extend the half-life of other medications, particularly other protease inhibitors. The initial Pediatric Written Request was issued at a time when only few antiretroviral agents with formulations appropriate for pediatric administration were available. Although, RTV at the recommended doses is not widely used in clinical practice, dosing information in children > 1 month to _____ may be important for those who are unable to receive other protease inhibitor based antiretroviral agents.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No new chemistry and manufacturing data or animal pharmacology and toxicology data were submitted with this sNDA. Please refer to section 5.5 for a summary of the pharmacokinetic data. Please also refer to Dr. Derek Zhang's review for a detail review of the pharmacokinetic data.

4 SUMMARY OF CLINICAL FINDINGS

4.1 Brief Overview of Clinical Program

Trade Name: Norvir (ritonavir)

Class: Protease Inhibitor

Formulation: Oral Solution

Dosage: Children > 1 month: 350 to 400 mg/m² twice daily by mouth and should not exceed 600 mg twice daily.

Trials: Two studies, PACTG 345 (pivotal) and PACTG 366 (supportive) were submitted.

PACTG 345 is a phase I/II, dose-finding, open-label study designed to assess the safety, tolerance, pharmacokinetics, and activity of RTV (350 mg/m² and 450 mg/m² twice daily) alone and in combination with lamivudine (4 mg/kg q 12h) and zidovudine (160 mg/m² q 8h) in HIV-1 infected infants and children.

PACTG 366 is a phase I/II, open-label, management algorithm for highly antiretroviral experienced HIV-infected children and adolescents between six months and 21 years of age with rapidly progressive or advanced HIV disease for whom current antiretroviral therapy was failing. Patients received RTV 350 mg/m² twice daily.

Number of patients enrolled in these trials:

Fifty HIV-1 infected children were enrolled in PACTG 345 and received at least one dose of RTV. In PACTG 366, 164 children six months to 21 years of age received antiretroviral regimen containing RTV (350 mg/m² BID). Fourteen of the 164 children were less than two years of age.

Indications studied: Treatment of HIV infection

4.2 Data Quality and Integrity

As previously stated, studies PACTG 345 (pivotal) and PACTG 366 (supportive) were submitted in support of this sNDA. At the request of the Division, the Division of Scientific Investigations (DSI) audited the clinical data from one site participating in PACTG 345. Specifically, Dr. Anne Gershon's site at the Department of Pediatrics, Columbia University, College of Physicians & Surgeons, New York, NY and the Internal Review Board (IRB) of the same institution were inspected. The selection of Columbia University for inspection was based on previous accusations in the 'lay' media stating researchers at this Institute enrolled foster children in HIV trials often without providing children with independent advocates to protect their rights and interests. In addition, DSI audited the analytical portion of study PACTG 366. The analytical portion of PACTG 345 study was not audited. DSI inspected the analytical site of PACTG 345 study ~~on numerous occasions for other bioequivalence studies and believes their analytical capabilities are adequate.~~ on numerous occasions for other bioequivalence studies and believes their analytical capabilities are adequate.

Findings from PACTG 366 analytical inspection:

In PACTG 366, pharmacokinetic data were obtained in 31 patients, 9 of whom were ≤ 2 years of age. The RTV pharmacokinetic data from these 9 children between 6 months and 2 years of age were submitted in part to fulfill the requirements as outlined in the Pediatric Written Request. The analytical portion of study 366 was conducted at the Pediatric ACTG Pharmacology Laboratory, the Department of Pediatrics, University of California at San Diego. Several major deficiencies were identified during the inspection of this site. Given these deficiencies, the data were not included for pharmacokinetic analysis (for more details see the report by Nilufer Tampal, Ph.D., from the Division of Scientific Investigations, CDER, FDA)

Findings from PACTG 345 Clinical and IRB Inspections:

Clinical inspection: The clinical inspection of the Department of Pediatrics at the Columbia University, College of Physicians & Surgeons did not identify any major deficiencies that would compromise the integrity of the study. Based on the DSI report the deficiencies noted were related to incorrect dose adjustments for lamivudine based on weight changes during the trial. These deficiencies do not compromise the RTV pharmacokinetic or safety data.

IRB inspection: The IRB inspection closed without issuance of a Form FDA 483. However, final determination by the DSI has not been made because the inspection report has not been received from the field investigator.

Conclusions/recommendations based on DSI findings :

Given the DSI IRB inspection report is not final, we also reviewed the data from PACTG 345 and 366 taking into consideration the worst case scenario, that is eliminating the pharmacokinetic data from PACTG 366 and the pharmacokinetic and safety data from the four subjects enrolled in PACTG 345 by Dr. Gershon. Of note, the pharmacokinetic data from PACTG 366 were supportive. Pediatric Exclusivity determination and dosing recommendations could be based on the pharmacokinetic and safety data from PACTG 345 alone. Specifically, Study PACTG 345 enrolled 50 HIV-infected pediatric subjects between one month and two years of age and pharmacokinetic results are available for 41 of the 50 patients:

1 month to < 3 months: 20 subjects (pharmacokinetic data available from 18 subjects)
3 months to < 6 months: 15 subjects (pharmacokinetic data available from 10 subjects)
6 months to < 2 years: 15 subjects (pharmacokinetic data available from 13 subjects)

Table. Data from the four infants enrolled at Columbia University Medical Center in study PACTG 345.

Patient I.D.	Age group	Pharmacokinetic data available
410424	3 months to < 6 months	Yes
410425	3 months to < 6 months	No
410436	1 month to < 3 months	Yes
411027	3 months to < 6 months	Yes

If the pharmacokinetic and safety data from the four children enrolled at Dr. Gershon's site were excluded the following data are available for review:

1 month to < 3 months: 19 (pharmacokinetic data available from 17 subjects)
3 months to < 6 months: 12 (pharmacokinetic data available from 8 subjects)
6 months to < 2 years: 15 (pharmacokinetic data available from 13 subjects)

Although no specific numbers are cited in the original Written Request, it is noteworthy that the number of patients with complete pharmacokinetic data from PACTG 345 after elimination of data from the four children enrolled at Columbia University Medical Center exceeds the minimal number of patients needed for pharmacokinetic evaluation cited in the current Written Request template:

6 weeks to < 6 months: 6

6 months to < 2years: 6

Overall, these findings clearly indicate that exclusion of the pharmacokinetic data from PACTG 366 study or exclusion of the pharmacokinetic data from the four patients enrolled in PACTG 345 at Dr. Greshon's site does not have any impact on the pediatric exclusivity determination, dosing recommendations or approvability of this sNDA.

4.3 Compliance with Good Clinical Practices

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of patients.

4.4 Financial Disclosures

The two studies submitted in this sNDA were evaluated for financial conflict of interest among investigators. The PACTG sent multiple communications to all investigators affiliated with studies PACTG 345 and PACTG 366 and asked them to complete and return the financial disclosure form. Despite multiple requests four of the 18 investigators affiliated with PACTG 345 and 18 of the 49 investigators affiliated with PACTG 366 did not return the financial disclosure form. Each of the four investigators affiliated with PACTG 345 who did not return the financial disclosure form enrolled 1 to 3 patients and their participation does not appear to bias the clinical study results.

Dr. Chadwick, the Protocol Vice Chair for PACTG 345 who was also directly involved in the treatment of patients at Children's Memorial Hospital, Chicago, IL, disclosed that she holds more than \$25,000 financial interest in Abbott Laboratories because her husband is employed by Abbott Laboratories. Dr Chadwick's site enrolled 3 subjects and is not expected to bias the clinical study outcome.

5 REVIEW OF CLINICAL STUDY RESULTS

5.1 Review Methods

The applicant submitted data from two clinical trials conducted by the Pediatric AIDS Clinical Trial Group (PACTG) in response to the final amended Pediatric Written Request. Study

PACTG 345 is the main study submitted to support the Pediatric Exclusivity recommendations in children > 1 month. Additional data supporting the clinical use of RTV were submitted from study PACTG 366. This review focused on the pharmacokinetic, activity, and safety data from pediatric patients > 1 month to enrolled in PACTG 345. Summaries of the analyses are presented in the sections below. Review of PACTG 366 study focused on safety and efficacy data in children < 2 years of age. The safety and efficacy results were consistent with those observed in PACTG 345 and from other RTV studies and therefore are not presented in detail in this review. Of note, only 14 patients less than two years of age were enrolled in PACTG 366. The safety data in children greater than two years of age are consistent with the current package insert. No new or unexpected safety findings were identified and therefore are not discussed in this review in detail.

5.2 Study Design

Study PACTG 345:

This is a phase I/II, dose-finding, open-label study designed to assess the safety, tolerance, pharmacokinetics, and activity of RTV alone and in combination with lamivudine (4 mg/kg q 12h) and zidovudine (160 mg/m² q 8h) in HIV-1 infected infants and children. The study includes 2 cohorts. In cohort I patients received 350 mg/m² BID RTV. The choice of the 350 mg/m² dose was based on anticipated RTV exposures similar to the 600 mg dose BID adult dose and preliminary data from older children in the National Cancer Institute study. Based on the pharmacokinetic data from patients in cohort I, the RTV dose in cohort II was increased to 450 mg/m² BID. Patients were stratified by age in each dose cohort as follows:

- Group I: > 6 months to 2 years, documented HIV-infected infants. On Day 0, a single dose of RTV was administered and pharmacokinetic parameters were assessed. RTV q 12h monotherapy then began 12 hours after the single dose. On Day 7, 3TC and ZDV were added.
- Group II: 3 months to 6 months, documented HIV-infected. Dosing was the same as Group I.
- Group IIIA: 4 weeks to ≤ 10 weeks. On Day 0, a single dose of RTV was administered and pharmacokinetic parameters were assessed. RTV, 3TC, and ZDV combination therapy was then started once RTV PK results were available (Day 7-10) and if the infant was either HIV-infected or was presumed HIV-infected.
- Group IIIB: 1 month to < 3 months, HIV-infected or presumed HIV-infected. This group was created to replace infants enrolled in Group IIIA who were not HIV-infected or presumed to have HIV-1 infection. On Day 0, these infants started on RTV, 3TC, and ZDV combination treatment.

All patients were to receive treatment for 104 weeks. If a patient's viral load was < 400

copies/mL at the end of 104-week study period, the patient was eligible to extend treatment for additional 104 weeks.

Patients were followed for safety and efficacy every four weeks to Week 104, every 12 weeks from Week 104 to Week 200, and then at Week 208.

A total of 50 HIV-infected children between 1 month (4 weeks) and 2 years of age were enrolled in this study; seventeen patients were enrolled in Cohort I (350 mg/m² BID) and the remaining 33 in Cohort II (450 mg/m² BID). The age distribution of the enrolled patients was as follows:

1 month to < 3 months: 20 (pharmacokinetic data available from 18 patients)
3 months to < 6 months: 15 (pharmacokinetic data available from 10 patients)
6 months to < 2 years: 15 (pharmacokinetic data available from 13 patients)

Pharmacokinetic data are available for 41 of the 50 enrolled patients.

Disposition and baseline characteristics of patients:

In cohort I, 59% were male and 65% were black, non-Hispanic patients. In cohort II, 33% were male and 70% were black, non-Hispanic patients. The median CD4 cell count was 2399 cells/μL in cohort I compared to 1579 cells/μL in cohort II. The median baseline HIV RNA was similar between cohort I and II and was 5.3 log₁₀ copies/mL.

In cohort I, 10 of the 17 patients (59%) prematurely discontinued study treatment: 6 (35%) after reaching a virologic endpoint, 3 (18%) due to intolerability, and 1 (6%) due to growth retardation.

In cohort II, 22 of the 33 patients (67%) prematurely discontinued study treatment: 14 (42%) after reaching a virologic endpoint, 3 (9%) due to intolerability, 2 (6%) due to treatment toxicity, 2 (6%) due to parent/guardian request, and 1 (3%) due to a study team decision related to difficulties in obtaining the blood samples.

Overall, 26/50 (52%) patients remained on study beyond 52 weeks and 21 (42%) remained on study for at least 104 weeks. The majority of patients (20/32; 63%) prematurely discontinued study treatment because they met the protocol specified virologic endpoint (HIV RNA > 400 copies/mL at or after Week 16 confirmed on repeat testing)

Study PACTG 366

This is a phase I/II, open-label, management algorithm for highly antiretroviral experienced HIV-infected children and adolescents between 6 months and 21 years of age with rapidly progressive or advanced HIV disease for whom current antiretroviral therapy was failing. Of the 201 enrolled patients, 164 received antiretroviral regimens containing RTV (350 mg/m² BID). The age distribution of the 164 enrolled patients who received antiretroviral regimen containing RTV was the following:

< 2 years: 14
2 to 6 years: 70
7 to 12 years: 55
≥ 13 to 21 years: 25

The majority of patients in this study were black, non Hispanic (64%) or Hispanic (26%).

5.3 Efficacy Results

In Study PACTG 345 no statistically significant differences were noted between Cohorts I and II during the first 104 weeks of follow-up with respect to HIV-1 RNA levels, CD4 cell count or CD4 percentage. Of note, no child met the protocol specified criteria for virologic failure prior to Week 16. The major virologic failure criterion in this study was HIV RNA > 400 copies/mL at or after Week 16. At Week 48, 8/17 (47%) of patients from Cohort I and 22/33 (67%) of patients from Cohort II had confirmed HIV-1 RNA levels > 400 copies/mL or treatment discontinuation. At Week 104, the patients from Cohorts I and II who had HIV-1 RNA levels > 400 copies/mL or treatment discontinuation were 9/17 (53%) and 23/33 (70%), respectively.

Analyses of CD4 cell count and CD4 percentage were restricted to measurements obtained while the patient was on study treatment and, after Week 16, prior to confirmed HIV-1 RNA levels > 400 copies/mL. In a non-randomized comparison of Cohorts I and II, no significant differences were noted in the median change in CD4 percentage from baseline to Week 48 or from baseline to Week 104.

It is important to keep in mind this is a small non-randomized study, and potential differences in demographic and baseline characteristics and changes in patient management may have confounded the comparisons between the two cohorts. In addition, the study was not designed to show efficacy (as assessed by HIV-RNA and CD4) differences between RTV dosing regimens, but to provide pharmacokinetic, safety, and activity data in children in order to determine an appropriate dosing regimen. One should also keep in mind that from a regulatory perspective, a pediatric dosing regimen may be approved if it is supported by efficacy in well-controlled studies in adults and by data identifying a dose that achieves a similar pharmacokinetic profile. Nevertheless, RTV has demonstrated activity in this population.

5.4 Safety Results

Overall, the toxicity profile of RTV seen during the clinical trial PACTG 345 appears similar to that observed in adults. No statistically significant differences were noted between Cohorts I and II with respect to the proportion of patients experiencing toxicities related to or possibly related to study treatment during the 104 weeks of follow-up [41% (7/17) vs. 27% (9/33)]. The most frequently reported Grade 2-4 adverse events and clinical laboratory abnormalities considered related/possibly related to study treatment were vomiting (12%; 6/50) and neutropenia (10%;

5/50). Potentially life-threatening, Grade 4 toxicities were experienced by 5 patients in Cohort II (RTV 450 mg/m²), while no patient in Cohort I experienced Grade 4 toxicity. These events were elevated ALT and AST levels (in the same child), anemia, abnormal glucose level, neutropenia and thrombocytopenia. Three of these Grade 4 events (affecting 2 children) were considered possibly related to study treatment and the other three Grade 4 events were considered not treatment related.

Grade 3-4 laboratory abnormalities were experienced by 24% (4/17) of patients in Cohort I and by 45% (15/33) of patients in Cohort II. The following Grade 3-4 laboratory abnormalities occurred in at least 2 patients: elevated amylase (12%; 6/50), neutropenia (8%; 4/50), sodium serum altered (8%; 4/50), and anemia (4%; 2/50).

Because RTV was a part of combination antiretroviral therapy, it is difficult to determine the exact contribution of RTV to any clinical or laboratory toxicities. It noteworthy, that many of the approved antiretroviral drugs have overlapping toxicities. Therefore, it is possible that drugs such as zidovudine may have contributed to neutropenia or anemia in some patients.

5.5 Pharmacokinetic Results

Pharmacokinetic data were obtained in 41 of the 50 patients enrolled in PACTG 345 study:

1 month to < 3 months: 18 (Cohort I: 6; Cohort II: 12)
3 months to < 6 months: 10 (Cohort I: 2; Cohort II: 8)
6 months to < 2 years: 13 (Cohort I: 6; Cohort II: 7)

A full complement of pharmacokinetic measurements was drawn on Day 1 and at Week 4 in Cohort I and after one and four weeks in Cohort II. Analyses of these measurements showed that in children > 1 month to 2 years of age higher RTV exposures were not evident with 450 mg/m² BID dose compared to 350 mg/m² BID dose. Study PACTG 345 also showed that RTV exposures after 350 or 450 mg/m² BID dosing were similar to that previously observed in older children after 250 to 350 mg/m² BID dosing with the exception that steady-state trough concentrations were somewhat lower in children < 2 years. The 250 and 350 mg/m² BID dosing in older children resulted in 58% and 33% higher C_{trough,ss} values, respectively, compared to the C_{trough,ss} values observed after 350 or 450 mg/m² BID dosing in children less than two years of age. Based on these data, and despite the high degree of variability in RTV exposure observed in younger children, a dose regimen up to 350 to 400 mg/m² BID is recommended for children > 1 month of age.

As previously stated, given the DSI IRB report is not final, we also reviewed the pharmacokinetic data without including the data from the four patients enrolled in PACTG 345 at the site of Columbia University Medical Center. The analyses showed that exclusion of these data has no impact on the overall conclusions of this review. For more details please see the review by Derek Zhang, the Clinical Pharmacology and Biopharmaceutics reviewer.

6 OVERALL ASSESSMENT

6.1 Conclusions

There is a need for pediatric use information for many of the recently approved antiretroviral drugs. Children have less treatment options than adults due to lack of pediatric formulations and information to guide clinicians in dosing HIV-infected children.

This supplement includes pharmacokinetic, safety, and activity data from children > 1 month of age who had received two dose levels of RTV. After a thorough review, the review team agrees that the submitted data in this supplement are adequate to approve dose recommendations for the use of RTV in children > 1 month of age. The recommended dose of RTV in children > 1 month is 350 to 400 mg/m² twice daily and will be included in the product label.

With respect to safety considerations, there were no unexpected adverse events. The overall adverse event profile of RTV in children appears similar to that observed in adults.

6.2 Labeling Review

CLINICAL PHARMACOLOGY

This section was modified to include pharmacokinetic data in children 1 month to 2 years of age. The new Clinical Pharmacology section for Pediatric Patients reads as follows:

Pediatric Patients

Steady-state pharmacokinetics were evaluated in 37 HIV infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m² twice-daily to 400 mg/m² twice daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses 350 and 450 mg/m² twice daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m²) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m² twice daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m² twice daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m² twice daily compared to the 350 mg/m² 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/m² twice daily were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice daily.

PRECAUTIONS

The following information was added under the section of Pediatric Use subsection:

Pediatric Use

In HIV-infected patients age > 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.

ADVERSE REACTIONS

The following information was added under the section of Pediatric Use subsection. Of note, the treatment-emergent adverse events and laboratory abnormalities shown in the label reflect the summary of the adverse events and laboratory abnormalities observed in pediatric studies M95-310, PACTG 366, and PACTG 345.

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 $\geq 2\%$ of pediatric patients enrolled in NORVIR clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in $\geq 3\%$ 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%).

DOSAGE AND ADMINISTRATION

The section of Pediatric Patients has been modified to include dosing recommendations for children > 1 month to The new Dosage and Administration section for Pediatric Patients is:

Pediatric Patients

Ritonavir should be used in combination with other antiretroviral agents (see General Dosing Guidelines). The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m² twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. If patients do not tolerate 400 mg/m² 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.

Pediatric Dosage Guidelines¹

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 can be calculated with the following equation:

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

Andreas Pikis, M.D.
 Medical reviewer

Concurrences:
 HFD-530/ActTL/Kstruble
 HFD-530/DepDir/JMurray

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Kimberly Struble
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10/6/2005 11:07:30 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUGS AND PRODUCTS

DATE: June 24, 2005

FROM: Medical Officer, HFD-530

SUBJECT: Study PACTG 345 and the Columbia University site

TO: NDA 20-659/SN034

On April 6, 2005, Abbott Laboratories submitted clinical study data for two trials (PACTG 345 and PACTG 366) conducted by the Pediatric AIDS Clinical Trial Group (PACTG) in response to a Pediatric Written Request for Norvir and in support of Pediatric Exclusivity. The Division presented the submission to the Pediatric Exclusivity Board meeting on June 14, 2005. The Pediatric Exclusivity Board members agreed with the Division and concluded that the applicant provided an adequate response to the Written Request. At the time of the meeting, the Division was aware of allegations against the Columbia University site and provided to the Pediatric Exclusivity Board the summary findings from CDER's Division of Scientific Investigations (DSI) inspection regarding Columbia University's involvement in the PACTG study 377 (DSI report dated 11/05/04). The report enumerates other PACTG studies conducted at the Columbia University site (PACTG 218, 253, 265, 292, 299, 345, 377, and 402). The summary findings regarding the inspection of PACTG 377 are as follows:

“the clinical investigator did not enroll subjects (children who were wards of the state in clinical trial) after the effective date of the revised regulations of 21 CFR 50.56 dated April 2001. Therefore, this complaint (857) will be closed and no follow up is necessary at this time.”

A few days after the Pediatric Exclusivity board meeting, a letter issued by the Office for Human Research Protections (OHRP) (dated May 23, 2005) finding noncompliance in research involving foster children in studies affiliated with Columbia University Medical Center came to our attention. PACTG 345, the major study submitted by Abbott Laboratories in support for the pediatric exclusivity for Norvir, was one of the studies cited in the OHRP letter. Similar allegations involving foster children in studies affiliated with Columbia University Medical Center were made in the past. In fact, the Division of Scientific Investigations (DSI) conducted an investigation between August 19 and 27, 2004, to evaluate the research and to ensure that the rights, safety, and welfare of the foster children enrolled in the AIDS studies affiliated with Columbia University Medical

Center were protected. As mentioned above regarding the 11/05/04 DSI summary findings regarding PACTG 377, the DSI concluded that investigators at Columbia University Medical Center adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Because of the nature of the findings cited in the OHRP letter the Division again contacted the DSI and asked for their opinion on the OHRP letter. In addition, we reviewed the data taking into consideration the scenario where data from patients enrolled at Columbia University Medical Center were eliminated from the study analysis, would there be sufficient amount of data to support exclusivity. In our review, we found seven infants enrolled at Columbia University Medical Center; four patients in study PACTG 345 and three in the supportive PACTG 366 study.

Study PACTG 345:

Study PACTG 345 enrolled 50 HIV-infected pediatric subjects between one month and two years of age and pharmacokinetic results are available for 41 of the 50 patients:

- 1 month to < 3 months: 20 subjects (pharmacokinetic data available from 18 subjects)
- 3 months to < 6 months: 15 subjects (pharmacokinetic data available from 10 subjects)
- 6 months to < 2 years: 15 subjects (pharmacokinetic data available from 13 subjects)

Table 1. Data from the four infants enrolled at Columbia University Medical Center in study PACTG 345.

Patient I.D.	Age group	Pharmacokinetic data available
410424	3 months to < 6 months	Yes
410425	3 months to < 6 months	No
410436	1 month to < 3 months	Yes
411027	3 months to < 6 months	Yes

If we eliminate data from these four infants, we still have safety and pharmacokinetic data for the following age ranges:

- 1 month to < 3 months: 19 (pharmacokinetic data available from 17 subjects)
- 3 months to < 6 months: 12 (pharmacokinetic data available from 8 subjects)
- 6 months to < 2 years: 15 (pharmacokinetic data available from 13 subjects)

Study PACTG 366:

PACTG 366, a supportive study not listed in the OHRP letter, enrolled 201 patients aged six months to 21 years with rapidly progressive or advanced HIV disease for whom antiretroviral therapy was failing. Of the 201 enrolled patients, 164 received antiretroviral regimens containing ritonavir. Pharmacokinetic data are available in 31 patients, nine of whom are \leq 2 years of age. It was found that only three children were enrolled by Columbia University Medical Center.

NDA 20-659
N-034

Table 2. Data from the three patients enrolled at Columbia University Medical Center in study PACTG 366.

Patient I.D.	Age (years)	Pharmacokinetic data available
410154	6.0	No
410310	3.1	No
411009	0.56	Yes

Therefore, PACTG 366 provides pharmacokinetic data for an additional 8 subjects aged six months to two years.

Although no specific numbers were cited in the original Written Request, it is noteworthy that the number of subjects with complete pharmacokinetic data exceeds the minimal number of subjects needed for pharmacokinetic evaluation as cited in the current Written Request template for drugs indicated to treat HIV infection (available at http://www.fda.gov/cder/pediatric/HIV2_template.htm).

6 weeks to < 6 months: 6 subjects

6 months to < 2 years: 6 subjects

These findings clearly indicate that based on all currently available information, exclusion of data from the seven patients enrolled at Columbia University Medical Center will not have any impact on the adequacy of the applicant's response to the Norvir's Written Request. These findings have been reviewed with the Clinical Pharmacology reviewer, Dr. Derek Zhang, for this Norvir pediatric supplement. The clinical and pharmacology reviewers determined if data from these seven patients were excluded, sufficient data still exist to conclude that the applicant provided a fair response to the Norvir Pediatric Written Request. The Division will continue to work with DSI to further evaluate the Columbia University study site.

Andreas Pikis, M.D.
Medical reviewer, DAVDP

Concurrences:
HFD-530/ActTL/KStruble
HFD-530/Dir/DBirnkrant

CC
HFD-530/TL/KMarcus
HFD-530/DepDir/JMurray
ODE-4/DepDir/ECox
ODE-4/Dir/MGoldberger

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Andreas Pikis
8/1/05 06:21:24 PM
MEDICAL OFFICER

Kimberly Struble
8/2/05 11:40:02 AM
MEDICAL OFFICER

Debra Birnkrant
8/3/05 01:19:28 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-659 / S-034

20-945 / S-017

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-659 (oral solution) 20-945 (capsule)	Submission Date(s): 04-06-2005
Brand Name	Norvir
Generic Name	Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Abbott
Other NDA(s)	20-680 (original capsule; no longer marketed)
Relevant IND(s)	43-718
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Indication	Treatment of HIV-1 infection

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has concluded that the clinical pharmacology information submitted to this NDA supplement is adequate to support the claim for Pediatric Exclusivity for Norvir and to make the relevant labeling revisions. Based on the submitted pharmacokinetic data, it is acceptable to expand the pediatric age range from > 2 years of age to > 1 month of age. The dosing regimen for HIV-infected pediatric patients does not change (350 to 400 mg/m² BID).

1.2 Post Marking Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Application Contents

Two studies provide pharmacokinetic data in HIV infected patients <2 years old of age.

Study PACTG 345 is the main study to support the Pediatric Exclusivity claim. The ritonavir dose regimens studied were 350 and 450 mg/m² BID. The number of subjects with pharmacokinetic data in each age group are as follows:

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Derek Zhang
2/24/2006 11:02:38 AM
BIOPHARMACEUTICS

Kellie Reynolds
2/24/2006 11:07:40 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-659 / S-034

20-945 / S-017

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



ABBOTT

ORIGINAL

Global Pharmaceutical Regulatory Affairs

Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

RECEIVED

SEP 28 2005

CDER White Oak DR 1

September 23, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Viral Drug Products
5901-B Ammendale Road
Beltsville, Maryland 20705

RECEIVED

SEP 26 2005

CDR / CDER

NDA SUPPL AMENDMENT

Re: **NORVIR**
NDA 20-945/S-016
NDA 20-659/S-033

- SLK-033 - BL

AMENDMENT TO A PENDING APPLICATION

Dear Sir or Madam:

Reference is made to our Approved New Drug Applications for Norvir (ritonavir capsules) and Norvir (ritonavir oral solution). Reference is also made to the August 12, 2005 approvable letter for NDA 20-945/S-016 and NDA 20-659/S-033 requesting submission of revised draft labeling in response to FDA labeling comments sent on August 11, 2005.

The purpose of this submission is to respond to FDA's August 11, 2005 correspondence. Abbott has incorporated all labeling changes requested by FDA in the August 11, 2005 correspondence. In addition, revisions have been made regarding coadministration of saquinavir/ritonavir with rifampin (see Precautions- Drug Interactions - Table 6 and Patient Package Insert). The proposed wording on coadministration of saquinavir/ritonavir with rifampin is based on a change made by Roche to the Invirase (saquinavir mesylate) package insert, approved by FDA on September 8, 2005. This submission contains:

1. Highlighted draft labeling incorporating all changes (including the original changes from NDA 20-945/S-016 and NDA 20-659/S-033, dated February 11, 2005, the changes submitted July 14, 2005 and from this amendment.
2. A clean copy of the draft labeling incorporating all changes.

Only a copy of this cover letter is being submitted to NDA 20-659.

Division of Anti-Viral Drug Products
NDA 20-945/S-016; NDA 20-659/S-033
September 23, 2005
Page 2

This submission is being provided electronically. It was created in accordance with the FDA Guidances for Industry: Providing Regulatory Submissions in Electronic Format -General Considerations, IT2 (January 1999), and Providing Regulatory Submissions to in Electronic Format - NDAs, IT3 (January 1999). The submission is contained on 1 CD comprising less than 5 megabytes of space. The content of the CD was checked for viruses using McAfee VirusScan Enterprise 7.1 and determined to be virus free.

If you have any questions regarding this submission, or if you need any additional information, please feel free to contact me at the number listed below. Thank you for your consideration in this matter.

Sincerely,



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