

Nelfinavir Tablets
NELVIR

COMPOSITION

Each uncoated tablet contains Nelfinavir mesylate equivalent to Nelfinavir 250 mg

DESCRIPTION

NELVIR (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease.

PHARMACOLOGY

Pharmacodynamics

Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Pharmacokinetics

The pharmacokinetic properties of nelfinavir were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the two groups.

Absorption: Pharmacokinetic parameters of nelfinavir (area under the plasma concentration-time curve during a 24-hour period at steady-state [AUC_{24}], peak plasma concentrations [C_{max}], morning and evening trough concentrations [C_{trough}]) from a pharmacokinetic study in HIV-positive patients after multiple dosing with 1250 mg (five 250 mg tablets) twice daily (BID) for 28 days (10 patients) and 750 mg (three 250 mg tablets) three times daily (TID) for 28 days (11 patients) are summarized in Table 1.

Table 1. Summary of a Pharmacokinetic Study in HIV-positive Patients with Multiple Dosing of 1250 mg (five 250 mg tablets) BID for 28 days and 750 mg (three 250 mg tablets) TID for 28 days

Regimen	AUC₂₄ mg.h/L	C_{max} mg/L	C_{trough} Morning mg/L	C_{trough} Afternoon or Evening mg/L
1250 mg BID	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
750 mg TID	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5

data are mean ± SD

The difference between morning and afternoon or evening trough concentrations for the TID and BID regimens was also observed in healthy volunteers who were dosed at precisely 8- or 12-hour intervals.

In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation. Under fasted conditions (n=27), the AUC and C_{max} were 34% and 24% higher, respectively, for the 625 mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625 mg tablet; the C_{max} was comparable for both formulations. In HIV-1 infected subjects (N = 21) receiving multiple doses of 1250 mg BID under fed conditions, the 625 mg formulation was bioequivalent to the 250 mg formulation based on similarity in steady state exposure (C_{max} and AUC). Table 2 shows the summary of the steady state pharmacokinetic parameters (mean ± s.d.) of nelfinavir after multiple dose administration of 1250 mg BID (2 x 625 tablets) to HIV-infected patients (N = 21) for 14 days.

Table 2 Summary of the steady state pharmacokinetic parameters (mean ± s.d.) of nelfinavir after multiple dose administration of 1250 mg BID (2 x 625 tablets) to HIV-infected patients (N = 21) for 14 days.

Regimen	AUC ₁₂ mg.h/L	C _{max} mg/L	C _{min} mg/L
1250 mg BID	35.3 (16.4)	4.7 (1.9)	1.5 (1.0)

AUC₁₂: Steady state AUC

C_{max}: Maximum plasma concentration at steady state

C_{min}: Minimum plasma concentration at steady state

In healthy volunteers receiving a single 750 mg dose under fed conditions, nelfinavir concentrations were similar following administration of the 250 mg tablet and oral powder.

Effect of Food on Oral Absorption

Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of nelfinavir 250 mg tablets (5 tablets) under fasted or fed conditions (three different meals). In a second study, healthy volunteers received single doses of 1250 mg nelfinavir (5 x 250 mg tablets) under fasted or fed conditions (two different fat content meals). The results from the two studies are summarized in Table 3 and Table 4, respectively.

Table 3: Increase in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg nelfinavir (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C _{max} fold increase	Increase in T _{max} (hr)
125	20	n=21	2.2	2.0	1.00
500	20	n=22	3.1	2.3	2.00
1000	50	n=23	5.2	3.3	2.00

Table 4: Increase in Nelfinavir AUC, C_{max} and T_{max} in Fed Low Fat (20%) versus High fat (50%) State Relative to Fasted State Following 1250 mg nelfinavir (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C _{max} fold increase	Increase in T _{max} (hr)
500	20	n=22	3.1	2.5	1.8
500	50	n=22	5.1	3.8	2.1

Nelfinavir exposure can be increased by increasing the calorie or fat content in meals taken with **NELVIR**.

A food effect study has not been conducted with the 625 mg tablet. However, based on a cross-study comparison (n=26 fed vs. n=26 fasted) following single dose administration of nelfinavir 1250 mg, the magnitude of the food effect for the 625 mg nelfinavir tablet appears comparable to that of the 250 mg tablets. **NELVIR** should be taken with a meal.

Distribution: The apparent volume of distribution following oral administration of nelfinavir was 2-7 L/kg. Nelfinavir in serum is extensively protein-bound (>98%).

Metabolism: Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750 mg dose of ¹⁴C-nelfinavir. *In vitro*, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination: The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750 mg dose containing ¹⁴C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

Special Populations:

Hepatic Insufficiency

The steady-state pharmacokinetics of nelfinavir (1250 mg BID for 2 weeks) was studied in HIV-seronegative subjects with mild (Child-Pugh Class A; n=6) or moderate (Child-Pugh Class B; n=6) hepatic impairment. When compared with subjects with normal hepatic function, the C_{max} and AUC of nelfinavir were not significantly different in subjects with mild hepatic impairment but were increased by 22% and 62% respectively in subjects with moderate hepatic impairment. The steady-state pharmacokinetics of nelfinavir has not been studied in HIV-seronegative subjects with severe hepatic impairment. The steady-state pharmacokinetics of nelfinavir has not been studied in HIV-positive patients with any degree of hepatic impairment.

Renal Insufficiency

The pharmacokinetics of nelfinavir has not been studied in patients with renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Pediatrics

The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving nelfinavir three times or twice daily. The dosing regimens and associated AUC₂₄ values are summarized in Table 5.

Table 5. Summary of Steady-state AUC₂₄ of Nelfinavir in Pediatric Studies

Protocol no.	Dosing regimen ¹	N ²	Age	AUC ₂₄ (mg.hr/L) arithmetic mean ± SD
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1 ± 29.8
PACTG-725	55 (48-60) mg/kg BID	6	3-11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2 ± 19.2
PACTG-353	40 (14-56) mg/kg BID	10	6 weeks	44.1 ± 27.4
			1 week	45.8 ± 32.1

¹ Protocol specified dose (actual dose range)

² N: number of subjects with evaluable pharmacokinetic results

C_{trough} values are not presented in the table because they are not available for all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received nelfinavir 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC₂₄ was 9 to 121 mg.hr/L. Overall, use of nelfinavir in the pediatric population is associated with highly variable drug exposure. The high variability may be due to inconsistent food intake in pediatric

patients. (See **WARNINGS AND PRECAUTIONS: Pediatric Use, DOSAGE AND ADMINISTRATION**)

Geriatric Patients: The pharmacokinetics of nelfinavir have not been studied in patients over 65 years of age.

INDICATIONS

NELVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

DOSAGE AND ADMINISTRATION

Adults

The recommended dose is 1250 mg (five 250 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. **NELVIR** should be taken with a meal. Patients unable to swallow the 250 or 625 mg tablets may dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy liquid well, and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

Pediatrics

In children 2 years of age and older, the recommended oral dose of **NELVIR** 250 mg tablet is 45 to 55 mg/kg twice daily or 25 to 30 mg/kg three times daily. All doses should be taken with a meal. Doses higher than the adult maximum dose of 2500 mg per day have not been studied in children.

Tables 6 provide dosing guidelines for **NELVIR** tablets based on age and body weight.

Table 6: Dosing for Children ≥ 2 Years of Age (Tablets)

Body Weight		Twice Daily (BID) 45-55 mg/kg ≥ 2 years	Three Times Daily (TID) 25-35 mg/kg ≥2 years
		# of tablets (250 mg)	# of tablets (250 mg)
Kg.	Lbs.		
10 - 12	22 –26.4	2	1
13 – 18	28.6 – 39.6	3	2
19 – 20	41.8 – 44	4	2
≥21	≥ 46.2	4 – 5 ¹	3 ²
¹ For BID dosing, the maximum dose per day is 5 tablets			
² For TID dosing, the maximum dose per day is 3 tablets			

Hepatic Impairment: **NELVIR** can be used in patients with mild hepatic impairment without any dose adjustment. **NELVIR** should not be used in patients with either moderate or severe hepatic impairment (see **PHARMACOLOGY**: Special Populations).

CONTRAINDICATIONS

NELVIR is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Co-administration of nelfinavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 7.

Table 7: Drugs That Are Contraindicated With Nelfinavir

Drug Class	Drugs Within Class That Are Contraindicated With Nelfinavir
Alpha 1 –adrenoreceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone, Quinidine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
Neuroleptic	Pimozide
PDE5 inhibitors	Sildenafil (for treatment of pulmonary arterial hypertension)
Sedative/Hypnotics	Midazolam, Triazolam

WARNINGS AND PRECAUTIONS

ALERT: Find out about medicines that should not be taken with NELVIR.

General

Nelfinavir is principally metabolized by the liver. (See **DOSAGE AND ADMINISTRATION**) when administering this drug to patients with hepatic impairment.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In 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.

Resistance/Cross-Resistance

HIV cross-resistance between protease inhibitors has been observed.

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy including nelfinavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Drug Interactions

Nelfinavir is an inhibitor of CYP3A (cytochrome P3A). Co-administration of **NELVIR** and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMGCoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects (See **UNDESIRABLE EFFECTS**; Post-Marketing Experience). Caution should be exercised when inhibitors of CYP3A, including nelfinavir, are co-administered with drugs that are metabolized by CYP3A and that prolong the QT interval. Nelfinavir is metabolised by CYP3A and CYP2C19. Co-administration of **NELVIR** and drugs that induce CYP3A, or CYP2C19 such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Co-administration of **NELVIR** and drugs that inhibit CYP3A or CYP2C19, may increase nelfinavir plasma concentrations (see Table 8 and 9).

Concomitant use of **NELVIR** with lovastatin or simvastatin is not recommended. Caution should be exercised if **NELVIR** is used concurrently with other HMG-CoA reductase inhibitors that are also metabolised by the CYP3A pathway. The risk of myopathy

including rhabdomyolysis may be increased when protease inhibitors including nelfinavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil, or other PDE5 inhibitors, in patients receiving protease inhibitors, including **NELVIR**. Co-administration of these drugs is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in PDE5 inhibitors associated adverse events including hypotension, visual changes and priapism.

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

Table 8: Drugs That Should Not Be Co-administered With Nelfinavir

Drug Class: Drug Name	Clinical Comment
Alpha 1-adrenoreceptor antagonist: Alfuzosin	Potentially increased alfuzosin concentrations can result in hypotension.
Antiarrhythmics: Amiodarone, Quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias
Antimycobacterial: Rifampin	May lead to loss of virologic response and possible resistance to nelfinavir or other coadministered antiretroviral agents
Ergot Derivatives: Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Herbal Products: St. John`s wort (<i>hypericum perforatum</i>)	May lead to loss of virologic response and possible resistance to nelfinavir or other coadministered antiretroviral agents
HMG-CoA Reductase Inhibitors: Lovastatin, Simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis
Neuroleptic: Pimozide	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias
PDE5 inhibitor: sildenafil [for treatment of pulmonary arterial hypertension]	A safe and effective dose has not been established when used with NELVIR. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, prolonged erection, and syncope).

Proton Pump Inhibitors	Omeprazole decreases the plasma concentrations of nelfinavir. Concomitant use of proton pump inhibitors and nelfinavir mesylate may lead to a loss of virologic response and development of resistance.
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 9: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV- Antiviral Agents		
Protease Inhibitors:		Appropriate doses for these combinations, with respect to safety and efficacy, have not been established
Indinavir	↑ Nelfinavir ↑ Indinavir	
Ritonavir Saquinavir	↑ Nelfinavir ↑ Saquinavir	
Non-nucleoside Reverse Transcriptase Inhibitors:		
Delavirdine	↑ Nelfinavir ↓ Delavirdine	Appropriate doses for these combinations, with respect to safety and efficacy, have not been established
Nevirapine	↓ Nelfinavir (C _{min})	
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after nelfinavir (given with food)
Other Agents		
Anti-convulsants: carbamazepine Phenobarbital	↓ Nelfinavir	May decrease nelfinavir plasma concentrations. Nelfinavir may not be effective due to

		decreased nelfinavir plasma concentrations in patients taking these agents concomitantly
Anticonvulsant: Phenytoin	↓ Phenytoin	Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration
Anti-mycobacterial: Rifabutin	↑ Rifabutin ↓ Nelfinavir (750 mg TID) ↔ nelfinavir (1250 mg BID)	It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with NELVIR ; 1250 mg BID is the preferred dose of NELVIR when co-administered with rifabutin
PDE5 inhibitors: sildenafil, vardenafil, tadalafil.	↑ PDE5 inhibitors	<p>Concomitant use of PDE5 inhibitors and NELVIR should be undertaken with caution.</p> <p>May result in an increase in PDE5 inhibitor associated adverse events, including hypotension, syncope, visual disturbances, and priapism.</p> <p><u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u></p> <ul style="list-style-type: none"> • Use of sildenafil is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) [see CONTRAINDICATIONS]. <p>The following dose adjustments are</p>

		<p>recommended for use of tadalafil with nelfinavir: Coadministration of tadalafil in patients on NELVIR or coadministration of NELVIR in patients on tadalafil: Start at or adjust tadalafil to 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 24 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended. Use with increased monitoring for adverse events.</p>
<p>HMG-CoA Reductase Inhibitor:</p> <p>Atorvastatin</p> <p>Rosuvastatin</p>	<p>↑ Atorvastatin</p> <p>↑ Rosuvastatin</p>	<p>Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with NELVIR.</p>
<p>Immunosuppressants:</p> <p>cyclosporine</p> <p>tacrolimus</p> <p>sirolimus</p>	<p>↑ Immuno-suppressants</p>	<p>Plasma concentrations may be increased by NELVIR.</p>
<p>Narcotic Analgesic: Methadone</p>	<p>↓ Methadone</p>	<p>Dosage of methadone may need to be increased when co-administered with NELVIR.</p>

Oral Contraceptive: ethinyl Estradiol	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when oral contraceptives and NELVIR are co-administered.
Macrolide Antibiotic: Azithromycin	↑ Azithromycin	Dose adjustment of azithromycin is not recommended, but close monitoring for known side effects such as liver enzyme abnormalities and hearing impairment is warranted.
Inhaled/nasal steroid: Fluticasone	↑ Fluticasone	Concomitant use of fluticasone propionate and nelfinavir may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Antidepressant: Trazodone	↑ Trazodone	<p>Concomitant use of trazodone and nelfinavir may increase plasma concentrations of trazodone.</p> <p>Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as nelfinavir, the combination should be used with caution and a lower dose of trazodone should be considered.</p>

<p>Anti-gout colchicines</p>	<p>↑ colchicines</p>	<p>Treatment of gout flares – coadministration of colchicines in patients on NELVIR.</p> <p>0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout-flares– coadministration of colchicine in patients on NELVIR: If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial Mediterranean fever (FMF)– coadministration of colchicine in patients on NELVIR: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). Patients with renal or hepatic impairment should not be given colchicine with NELVIR.</p>
<p>Endothelin receptor antagonists: Bosentan</p>	<p>↑Bosentan</p>	<p>Coadministration of bosentan in patients on NELVIR or coadministration of NELVIR in patients on bosentan.</p> <p>Start or adjust bosentan to 62.5 mg once daily or every other day based</p>

		upon individual tolerability.
Inhaled beta agonist : Salmeterol	↑ Salmeterol	Concurrent administration of salmeterol with NELVIR is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Pregnancy

Pregnancy Category B

There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women taking nelfinavir. Because animal reproduction studies are not always predictive of human response, **NELVIR** should be used during pregnancy only if clearly needed.

Lactation

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving **NELVIR**.

Pediatric Use

The safety and effectiveness of nelfinavir have been established in patients from 2 to 13 years of age. The use of nelfinavir in these age groups is supported by evidence from adequate and well-controlled studies of nelfinavir in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, nelfinavir was found to be safe at the doses studied, but a reliably effective dose could not be established.

The following issues should be considered when initiating nelfinavir in pediatric patients:

- In pediatric patients ≥ 2 years of age receiving nelfinavir as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving a HIV RNA level <400 copies/mL through 48 weeks ranged from 26% to 42%.
- Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies.
- Highly variable drug exposure remains a significant problem in the use of nelfinavir in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing.

Study 556 was a randomized, double-blind, placebo-controlled trial with nelfinavir or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. Ninety four (67%) children were between 2-12 years, and 47 (33%) were < 2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm³ for all patients. The efficacy of nelfinavir measured by HIV RNA <400 at 48 weeks in children ≥ 2 years of age was 26% compared to 2% of placebo patients ($p=0.0008$). In the children < 2 years of age, only 1 of 27 and 2 of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and nelfinavir patients, respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, or d4T+3TC+NVP+NFV with NFV given on a TID schedule. The median age was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm³. Substudy PACTG 725 evaluated d4T+3TC+NFV with NFV given on a BID schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/mL at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving nelfinavir in BID or TID schedules.

Geriatric Use

Clinical studies of nelfinavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

UNDESIRABLE EFFECTS

The safety of nelfinavir was studied in over 5000 patients who received the drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving nelfinavir was diarrhea, which was generally of mild to moderate intensity.

Drug-related clinical adverse experiences of moderate or severe intensity in $\geq 2\%$ of patients treated with nelfinavir coadministered with d4T and 3TC (Study 542) for up to 48 weeks or with ZDV plus 3TC (Study 511) for up to 24 weeks are presented in Table 10.

Table 10: Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in $> 2\%$ of Patients.

Adverse Events	Study 511 24 weeks			Study 542 48 weeks	
	Placebo + ZDV/3TC (n=101)	500 mg TID nelfinavir + ZDV/3TC (n=97)	750 mg TID nelfinavir + ZDV/3TC (n=100)	1250 mg BID nelfinavir + d4T/3TC (n=344)	750 mg TID nelfinavir + d4T/3TC (n=210)
Digestive System					
Diarrhea	3%	14%	20%	20%	15%
Nausea	4%	3%	7%	3%	3%
Flatulence	0	5%	2%	1%	1%
Skin/Appendages					
Rash	1%	1%	3%	2%	1%

¹Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.

Adverse events occurring in less than 2% of patients receiving nelfinavir in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a whole: Abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain and redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS:** Fat redistribution).

Digestive system: Anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Hemic/Lymphatic System: Anemia, leucopenia and thrombocytopenia.

Metabolic/Nutritional System: Increases in alkaline phosphate, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.

Musculoskeletal System: Arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.

Nervous System: Anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paraesthesia, seizures, sleep disorder, somnolence and suicide ideation

Respiratory System: Dyspnea, pharyngitis, rhinitis, and sinusitis

Skin/Appendages: Dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria

Special Senses: Acute iritis and eye disorder

Urogenital System: Kidney calculus, sexual dysfunction and urine abnormality

Post-marketing Experience

The following additional adverse experiences have been reported from post marketing surveillance as at least possibly related or of unknown relationship to nelfinavir.

Body as a Whole: hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema)

Cardiovascular System: QTc prolongation, torsades de pointes

Digestive System: jaundice

Metabolic/Nutritional System: bilirubinemia, metabolic acidosis

Laboratory Abnormalities

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 11. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

Table 11: Percentage of Patients by Treatment Group with Marked Laboratory Abnormalities ¹ in > 2% of Patients

	Study 511			Study 542	
	Placebo + ZDV/3TC (n=101)	500 mg TID Nelfinavir + ZDV/3TC (n=97)	750 mg TID Nelfinavir + ZDV/3TC (n=100)	1250 mg BID Nelfinavir + d4T/3TC (n=344)	750 mg TID Nelfinavir + d4T/3TC (n=210)
Hematology					
Hemoglobin	6%	3%	2%	0	0
Neutrophils	4%	3%	5%	2%	1%
Lymphocytes	1%	6%	1%	1%	0
Chemistry					
ALT (SGPT)	6%	1%	1%	2%	1%
AST (SGOT)	4%	1%	0	2%	1%
Creatine Kinase	7%	2%	2%	NA	NA

¹ Marked laboratory abnormalities are defined as a shift from Grade 0 at baseline to at least Grade 3 or from Grade 1 to Grade 4

Pediatric Population

Nelfinavir has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults. The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leucopenia/neutropenia, rash, anorexia and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving nelfinavir in two of the larger treatment trials. Leucopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

OVERDOSAGE

Human experience of acute overdose with nelfinavir is limited. There is no specific antidote for overdose with nelfinavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since nelfinavir is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

PACKAGING INFORMATION

NELVIR----- Container of 100 tablets

Last updated: October 2010