

Zidovudine, Lamivudine and Nevirapine Tablet  
**DUOVIR-N**

**WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B, LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY AND SKIN REACTIONS**

**DUOVIR-N TABLET IS NOT INTENDED FOR USE IN PATIENTS WHO ARE JUST INITIATING THERAPY WITH NEVIRAPINE. DUOVIR-N TABLET SHOULD BE ADMINISTERED ONLY TO PATIENTS WHO HAVE RECEIVED ZIDOVUDINE + LAMIVUDINE (STANDARD DOSES) + NEVIRAPINE (200 mg O.D.) FOR 2 WEEKS AND HAVE DEMONSTRATED ADEQUATE TOLERABILITY TO NEVIRAPINE (SEE INDICATIONS; DOSAGE AND ADMINISTRATION).**

**ZIDOVUDINE, ONE OF THE COMPONENTS HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV-1 DISEASE (SEE WARNINGS AND PRECAUTIONS).**

**PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY. (SEE WARNINGS AND PRECAUTIONS). LACTIC ACIDOSIS AND HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE, AND OTHER ANTIRETROVIRALS. SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS AND PRECAUTIONS).**

**ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV -1 AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF DUOVIR-N. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE /ZIDOVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).**

**SEVERE, LIFE THREATENING, AND IN SOME CASES, FATAL HEPATOTOXICITY, PARTICULARLY IN THE FIRST 18 WEEKS, HAS BEEN REPORTED IN PATIENTS TREATED WITH NEVIRAPINE. IN**

SOME CASES, PATIENTS PRESENTED WITH NON-SPECIFIC PRODROMAL SIGNS OR SYMPTOMS OF HEPATITIS AND PROGRESSED TO HEPATIC FAILURE. THESE EVENTS ARE OFTEN ASSOCIATED WITH RASH. FEMALE GENDER AND HIGHER CD4<sup>+</sup> CELL COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4<sup>+</sup> CELL COUNTS >250 cells/mm<sup>3</sup>, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV-1 INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4<sup>+</sup> CELL COUNTS AND AT ANY TIME DURING TREATMENT. HEPATIC FAILURE HAS ALSO BEEN REPORTED IN PATIENTS WITHOUT HIV TAKING NEVIRAPINE FOR POST-EXPOSURE PROPHYLAXIS (PEP). USE OF NEVIRAPINE FOR OCCUPATIONAL AND NONOCCUPATIONAL PEP IS CONTRAINDICATED (SEE CONTRAINDICATIONS). PATIENTS WITH SIGNS OR SYMPTOMS OF HEPATITIS, OR WITH INCREASED TRANSAMINASES COMBINED WITH RASH OR OTHER SYSTEMIC SYMPTOMS, MUST DISCONTINUE NEVIRAPINE AND SEEK MEDICAL EVALUATION IMMEDIATELY (SEE WARNINGS AND PRECAUTIONS).

SEVERE, LIFE-THREATENING SKIN REACTIONS, INCLUDING FATAL CASES, HAVE OCCURRED IN PATIENTS TREATED WITH NEVIRAPINE. THESE HAVE INCLUDED CASES OF STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, AND HYPERSENSITIVITY REACTIONS CHARACTERIZED BY RASH, CONSTITUTIONAL FINDINGS AND ORGAN DYSFUNCTION. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF SEVERE SKIN REACTIONS OR HYPERSENSITIVITY REACTIONS MUST DISCONTINUE NEVIRAPINE AND SEEK MEDICAL EVALUATION IMMEDIATELY. TRANSAMINASE LEVELS SHOULD BE CHECKED IMMEDIATELY FOR ALL PATIENTS WHO DEVELOP A RASH IN THE FIRST 18 WEEKS OF TREATMENT. THE 14-DAY LEAD-IN PERIOD WITH NEVIRAPINE 200 mg DAILY DOSING HAS BEEN OBSERVED TO DECREASE THE INCIDENCE OF RASH AND MUST BE FOLLOWED (SEE WARNINGS AND PRECAUTIONS).

PATIENTS MUST BE MONITORED INTENSIVELY DURING THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE TO DETECT POTENTIALLY LIFE-THREATENING HEPATOTOXICITY OR SKIN REACTIONS. EXTRA VIGILANCE IS WARRANTED DURING THE FIRST 6 WEEKS OF THERAPY, WHICH IS THE PERIOD OF GREATEST RISK OF THESE EVENTS. DO NOT RESTART NEVIRAPINE FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC

**INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT.**

**COMPOSITION**

**DUOVIR-N Tablet**

Each film-coated tablet contains:

Lamivudine ..... 150 mg

Zidovudine ..... 300 mg BP

Nevirapine ..... 200 mg

**DOSAGE FORM**

Film-coated tablet

**DESCRIPTION**

**DUOVIR-N Tablet** are a combination of three drugs commonly used in the management of the Human Immunodeficiency Virus (HIV) infection. Both zidovudine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase (RT) of HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It acts by directly inhibiting RT.

Each tablet of **DUOVIR-N** contains half of the commonly prescribed daily doses of zidovudine, lamivudine and nevirapine. Usually, all three drugs are to be administered twice daily, permitting a fixed-dose combination to be formulated. With the availability of this combination formulation, patients may be better able to adhere to triple drug regimens, thereby enhancing compliance.

**PHARMACOLOGY**

**Pharmacodynamics**

**Lamivudine:** Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. 3TC-TP is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ .

**Zidovudine:** Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerase  $\alpha$  and  $\gamma$  and has been reported to be incorporated into the DNA of cells in culture.

**Nevirapine:** Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to RT and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the

enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$  or  $\delta$ ) are not inhibited by nevirapine.

### Pharmacokinetics in Adults

**Lamivudine:** The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low.

Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

**Zidovudine:** The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low.

Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

**Table 1: Pharmacokinetic Parameters\* for Lamivudine and Zidovudine in Adults**

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 $\pm$ 16	N=12	64 $\pm$ 10	n=5
Apparent volume of distribution (L/kg)	1.3 $\pm$ 0.4	N=20	1.6 $\pm$ 0.6	n=8
Plasma protein binding (%)	<36		<38	
CSF: Plasma ratio <sup>†</sup>	0.12 [0.04 to 0.47]	n=38 <sup>‡</sup>	0.60 [0.04 to 2.62]	N=39 <sup>§</sup>
Systemic clearance (L/hr/kg)	0.33 $\pm$ 0.06	N=20	1.6 $\pm$ 0.6	n=6
Renal clearance (L/hr/kg)	0.22 $\pm$ 0.06	N=20	0.34 $\pm$ 0.05	n=9
Elimination half-life (hr) <sup>#</sup>	5 to 7		0.5 to 3	

\* Data presented as mean  $\pm$  standard deviation except where noted.

<sup>†</sup> Median [range].

<sup>‡</sup> Children.

<sup>§</sup> Adults.

<sup>#</sup> Approximate range.

### Effect of Food on Absorption of Lamivudine/Zidovudine

Lamivudine/Zidovudine may be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of Lamivudine/Zidovudine with food was similar when compared to fasting healthy subjects 400 (n = 24).

### ***Nevirapine:***

#### ***Absorption and Bioavailability:***

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was  $93 \pm 9\%$  (mean  $\pm$  SD) for a 50 mg tablet and  $91 \pm 8\%$  for an oral solution. Peak plasma nevirapine concentrations of  $2 \pm 0.4 \mu\text{g/mL}$  ( $7.5 \mu\text{M}$ ) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough nevirapine concentrations of  $4.5 \pm 1.9 \mu\text{g/mL}$  ( $17 \pm 7 \mu\text{M}$ ), (n=242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid, the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure ( $\text{AUC}_{\tau}$ ) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

#### ***Distribution***

Nevirapine is highly lipophilic and is essentially non-ionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution ( $V_{\text{dss}}$ ) of nevirapine was  $1.21 \pm 0.09 \text{ L/kg}$ , suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10  $\mu\text{g/mL}$ . Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% ( $\pm 5\%$ ) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

#### ***Metabolism/Elimination***

*In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450

(oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of <sup>14</sup>C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A and CYP2B6 mediated metabolism leads to an approximately 1.5- to 2fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

## INDICATIONS

**DUOVIR-N** Tablet is indicated for the treatment of HIV infection, once patients have been stabilized on the maintenance regimen of nevirapine 200 mg b.i.d., and have demonstrated adequate tolerability to nevirapine.

Additional important information regarding the use of nevirapine for the treatment of HIV-1 infection is given below:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, **DUOVIR-N** Tablet should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm<sup>3</sup> or in adult males with CD4+ cell counts greater than 400 cells/mm<sup>3</sup> unless the benefit outweighs the risk (see **WARNINGS AND PRECAUTION**).
- The 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see **WARNINGS AND PRECAUTIONS; DOSAGE AND ADMINISTRATION**).
- If rash persists beyond the 14 day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once daily dosing regimen should not be continued beyond 28 days, after which an alternative regimen should be sought.

## DOSAGE AND ADMINISTRATION

### Adults

One tablet twice daily.

**DUOVIR-N Tablet** should not be administered to patients who have just initiated therapy with nevirapine. This is because an initial lead-in dosing of 200 mg nevirapine once daily for 2 weeks, along with the standard doses of lamivudine + zidovudine twice daily is recommended. Following this lead-in dose, a dose escalation (maintenance dose) to **DUOVIR-N Tablet** twice daily may be carried out in the absence of any hypersensitivity reactions (e.g. rash, liver function test abnormalities) (see **WARNINGS AND PRECAUTIONS**).

### Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at 2 weeks post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment (see **WARNINGS AND PRECAUTIONS**). In some cases, hepatic injury has progressed despite discontinuation of treatment.

### Dosage Adjustment

Because **DUOVIR-N Tablet** is a fixed-dose combination, they should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance <50 mL/min), or hepatic impairment, or those experiencing dose-limiting adverse events.

**DUOVIR-N Tablet** should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see **WARNINGS AND PRECAUTIONS**). Patients experiencing mild to moderate rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased or start therapy with **DUOVIR-N Tablet** until the rash has resolved (see **WARNINGS AND PRECAUTIONS**). If rash persists beyond the 14-day lead-in period, do not dose escalate to **DUOVIR-N Tablet** twice daily. The **DUOVIR-N Tablet** once-daily dosing regimen should not be continued beyond 28 days, after which an alternative regimen should be sought.

If a clinical (symptomatic) hepatic event occurs, nevirapine should be permanently discontinued and not be restarted after recovery (see **WARNINGS AND PRECAUTIONS**).

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200 mg nevirapine tablet daily for the first 14 days (lead-in) in combination with the lamivudine + zidovudine, followed by **DUOVIR-N** Tablet twice daily in the absence of any signs of hypersensitivity.

### **CONTRAINDICATIONS**

**DUOVIR-N** Tablet is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, anaphylaxis, Stevens-Johnson syndrome) to any of the components of the product.

**DUOVIR-N** Tablet is contraindicated in patients with moderate or severe (Childs Pugh Class B or C, respectively) hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

**DUOVIR-N** Tablet is also contraindicated for patients who are just initiating therapy with nevirapine. These patients require a lead-in dose of nevirapine 200 mg o.d., whereas this formulation contains the maintenance dose of nevirapine 200 mg b.i.d. (see **INDICATIONS**).

Nevirapine is contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens (see **WARNINGS AND PRECAUTIONS**).

### **WARNINGS AND PRECAUTIONS**

#### **Drug Interactions**

#### **Lamivudine and Zidovudine**

##### ***Antiretroviral Agents***

##### *Lamivudine*

*Zalcitabine*: Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine / zidovudine in combination with zalcitabine is not recommended.

##### *Zidovudine*:

*Stavudine*: Concomitant use of lamivudine / zidovudine with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

##### *Nucleoside Analogues Affecting DNA Replication*

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV-1; concomitant use of such drugs should be avoided.

### *Doxorubicin*

Zidovudine: Concomitant use of lamivudine /zidovudine with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

### *Hematologic/Bone Marrow Suppressive/Cytotoxic Agents*

Zidovudine: Co-administration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

### *Interferon- and Ribavirin-Based Regimens*

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin (see **WARNINGS AND PRECAUTIONS**).

### *Trimethoprim/Sulfamethoxazole (TMP/SMX)*

Lamivudine: No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX, such as those used to treat PCP.

### *Nevirapine*

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine.

Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 2. This data is based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are also listed in Table 1. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 2, additional clinical monitoring may be warranted when co-administering these drugs.

The *in vitro* interaction between nevirapine and the antithrombotic agent, warfarin, is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When

warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

**Table 2: Established Drug Interactions: Use with Caution. Alteration in Dose or Regimen May Be Needed due to Drug Interaction Studies**

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Atazanavir/Ritonavir	↓Atazanavir ↑Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure.
Clarithromycin	↓Clarithromycin ↑↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> , overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this

		combination. (see <b>WARNINGS AND PRECAUTIONS</b> ).
Ethinyl estradiol and Norethindrone	↓Ethinyl estradiol  ↓ Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Fosamprenavir	↓ Amprenavir  ↑ Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir /Ritonavir	↓ Amprenavir  ↑ Nevirapine	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily.
Indinavir	↓Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage

		of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓ Lopinavir	<p>A dose increase of lopinavir/ritonavir tablets to 500/125 mg twice daily is recommended when used in combination with nevirapine.</p> <p>A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with nevirapine.</p> <p>In children, 6 months to 12 years of age receiving lopinavir/ritonavir solution, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those weighing 7 to &lt;15 kg; 11/2.75 mg/kg for those weighing 15 to 45 kg; and up to a maximum dose of 533/133 mg twice daily.</p> <p>Refer to the lopinavir/ritonavir</p>

		package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine.
Methadone	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.
Nelfinavir	↓ Nelfinavir M8 Metabolite ↓ Nelfinavir C <sub>min</sub>	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑↑ Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant

		administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.
Saquinavir /Ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.

**Table 3: Potential Drug Interactions:**

<b>Examples of drugs in which plasma concentrations may be decreased by co-administration with nevirapine</b>	
<b>Drug Class</b>	<b>Examples of Drugs</b>
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole  Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations.
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine

Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
<b>Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine</b>	
Antithrombotics	Warfarin  Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and nevirapine is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs. Co-administration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

### **Lamivudine and Zidovudine**

#### **Hematologic Toxicity/Bone Marrow Suppression**

Zidovudine, a component of **DUOVIR-N** Tablet has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. **DUOVIR-N** Tablet should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1000 cells/mm<sup>3</sup> or hemoglobin less than 9.5 g/dl (see **UNDESIRABLE EFFECTS**).

Frequent blood counts are strongly recommended in patients with advanced HIV-1 disease who are treated with **DUOVIR-N** Tablet. Periodic blood counts are recommended for other HIV - 1 -infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

#### **Myopathy**

Myopathy and myositis, with pathological changes similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine and, therefore, may occur with therapy with **DUOVIR-N** Tablet.

#### **Lactic Acidosis/Hepatomegaly With Steatosis**

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine and other antiretrovirals. A majority of these cases have

been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering zidovudine and lamivudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Cases have also been reported in patients with no known risk factors. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

## **Patients with HIV-1 and Hepatitis B Virus Co-infection**

### ***Post-Treatment Exacerbations of Hepatitis***

In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV) DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

### ***Important Differences Among Lamivudine-Containing Products***

Lamivudine and Zidovudine tablet contain a higher dose of the same active ingredient (lamivudine) than in Lamivudine-HBV Tablet. Lamivudine-HBV was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

### ***Emergence of Lamivudine-Resistant HBV***

In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B Virus variants associated with resistance to lamivudine has also been reported in HIV -1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B Virus.

## **Use with Other, Lamivudine - Zidovudine and/or Emtricitabine-Containing Products**

Lamivudine/Zidovudine should not be administered concomitantly with other lamivudine - or emtricitabine - containing products.

### **Use with Interferon- and Ribavirin-Based Regimens**

*In vitro* studies have shown that ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine/zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of lamivudine/zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Childs Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV -1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

### **Pancreatitis**

Lamivudine / Zidovudine should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with Lamivudine / Zidovudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see **UNDESIRABLE EFFECTS**).

### **Nevirapine**

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy or renal dysfunction.

**The first 18 weeks of therapy with nevirapine are a critical period during which intensive monitoring of patients is required to detect potentially life-**

**threatening hepatic events and skin reactions.** The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at 2 weeks post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see **DOSAGE AND ADMINISTRATION**).

### **Hepatotoxicity and Hepatic Impairment**

Severe, life threatening and, in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range: 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver enzyme tests.

**Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible.**

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, **DUOVIR-N Tablet** should be permanently discontinued and not restarted after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts  $>250$  cells/mm<sup>3</sup> had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts  $<250$  cells/mm<sup>3</sup> (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts  $>400$  cells/mm<sup>3</sup> (6.3% versus 1.2% for men with CD4 counts  $<400$  cells/mm<sup>3</sup>). However, all patients, regardless of gender, CD4 counts, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of symptomatic events later (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis, an unapproved use. Use of Nevirapine for occupational and non-occupational PEP is contraindicated (see **CONTRAINDICATIONS**).

Increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease. Nevirapine should not be administered to patients with moderate or severe (Childs Pugh Class B or C, respectively) hepatic impairment. (see **CONTRAINDICATIONS AND CLINICAL PHARMACOLOGY**).

### **Skin Reactions**

Severe and life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterized by rash, constitutional findings and organ dysfunction, including hepatic failure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to severe rash or rash accompanied by fever,

general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately. Nevirapine should not be restarted following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, transaminases should be measured immediately. Patients with rash-associated transaminase elevations should be permanently discontinued from nevirapine. (see **WARNINGS AND PRECAUTIONS**).

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day which has been shown to reduce the frequency of rash. Nevirapine should be discontinued if a patient experiences severe rash or any rash accompanied by constitutional findings. A patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200mg/day should have their nevirapine dose increased until the rash has resolved. The total duration of the once-daily lead-in-dosing period should not exceed 28 days at which point an alternative regimen should be sought (see **DOSAGE AND ADMINISTRATION**). Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reaction. Women appear to be at higher risk than men of developing rash with nevirapine.

In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in the incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine-associated rash is not recommended.

### **Resistance**

Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other NNRTIs, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross-resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

### **Lamivudine, Zidovudine and Nevirapine**

#### ***Immune Reconstitution Syndrome***

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine, zidovudine and

nevirapine. 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.

### ***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.

### ***Renal Impairment***

Reduction of the dosage of zidovudine, lamivudine and nevirapine is required in patients with impaired renal function. Additional doses of nevirapine are required for patients on dialysis. Since **DUOVIR-N** Tablet is a fixed-dose combination, they should not be prescribed for this patient population.

### ***Hepatic Impairment***

No dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Since zidovudine is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients.

It is not clear whether a dosing adjustment is needed for patients with mild to moderate hepatic impairment, because multiple dose pharmacokinetic data are not available for this population. However, patients with moderate hepatic impairment and ascites may be at risk of accumulating nevirapine in the systemic circulation. Caution should be exercised when nevirapine is administered to patients with moderate hepatic impairment. Nevirapine should not be administered to patients with severe hepatic impairment.

Increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease. Nevirapine should not be administered to patients with severe hepatic impairment.

Since **DUOVIR-N** Tablet is a fixed-dose combination, it should not be prescribed for this patient population.

### ***Pregnancy***

Lamivudine and zidovudine are classified under Category C, whereas nevirapine is classified under Category B. There are no adequate and well-controlled studies in pregnant women. **DUOVIR-N** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV -1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to embryotoxicity and fetal malformations (zidovudine), and increased embryoletality (lamivudine). Lamivudine/Zidovudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately equivalent administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

Severe hepatic events, including fatalities, have been reported in pregnant women receiving continual nevirapine therapy as part of a combination treatment of HIV infection. Regardless of pregnancy status, women with CD4 counts  $>250$  cells/mm<sup>3</sup> should not initiate **DUOVIR-N** Tablet unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women. (see **BOXED WARNING**).

### **Lactation**

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. Lamivudine, zidovudine and nevirapine are excreted in human breast milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving DUOVIR-N Tablet.**

### **Pediatric Use**

**DUOVIR-N** Tablet is not intended for use in pediatric patients.

### **Geriatric Use**

Clinical studies of Lamivudine, Zidovudine and Nevirapine did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

## **UNDESIRABLE EFFECTS**

### **Zidovudine and Lamivudine**

The following are the adverse reactions

- Hematologic toxicity, including neutropenia and anemia (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- Symptomatic myopathy (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**).
- Lactic acidosis and hepatomegaly with steatosis (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**).
- Acute exacerbations of hepatitis B (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**).
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C (see **WARNINGS AND PRECAUTIONS**)
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine (see **WARNINGS AND PRECAUTIONS**).
- Pancreatitis (see **WARNINGS AND PRECAUTIONS**).

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

**Lamivudine Plus Zidovudine Administered As Separate Formulations:**

In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected clinical and laboratory adverse events were observed (Table 4 and 5).

**Table 4: Selected Clinical Adverse Reactions (≥5% Frequency) in 4 Controlled Clinical Trials with Lamivudine 300 mg/day and Zidovudine 600 mg/day**

<b>Adverse Reaction</b>	<b>Lamivudine plus Zidovudine (n = 251)</b>
<b>Body as a Whole</b>	
Headache	35%
Malaise and fatigue	27%
Fever or chills	10%
<b>Digestive</b>	
Nausea	33%
Diarrhea	18%
Nausea and vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
<b>Nervous System</b>	

Neuropathy	12%
Insomnia and other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
<b>Respiratory</b>	
Nasal signs and symptoms	20%
Cough	18%
<b>Skin</b>	
Skin rashes	9%
<b>Musculoskeletal</b>	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in controlled clinical trials. (see **WARNINGS AND PRECAUTIONS**).

Selected laboratory abnormalities observed during therapy are listed in Table 5.

**Table 5: Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of Lamivudine 300 mg/day Plus Zidovudine 600 mg/day\***

Test (Abnormal Level)	Lamivudine plus Zidovudine
	% (n)
Neutropenia (ANC <750/mm <sup>3</sup> )	7.2% (237)
Anemia (Hgb <8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets <50,000/mm <sup>3</sup> )	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

\* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

## Observed During Clinical Practice

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, zidovudine, and/or lamivudine/zidovudine.

***Body as a Whole:*** Redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS, Fat Redistribution**).

***Cardiovascular:*** Cardiomyopathy.

***Endocrine and Metabolic:*** Gynecomastia, hyperglycemia.

***Gastrointestinal:*** Oral mucosal pigmentation, stomatitis.

***General:*** Vasculitis, weakness.

***Hemic and Lymphatic:*** Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

***Hepatic and Pancreatic:*** Lactic acidosis and hepatic steatosis, pancreatitis, post-treatment exacerbation of hepatitis B (see **WARNINGS AND PRECAUTIONS**).

***Hypersensitivity:*** Sensitization reactions (including anaphylaxis), urticaria.

***Musculoskeletal:*** Muscle weakness, CPK elevation, rhabdomyolysis.

***Nervous:*** Paresthesia, peripheral neuropathy, seizures.

***Respiratory:*** Abnormal breath sounds/wheezing.

***Skin:*** Alopecia, erythema multiforme, Stevens-Johnson syndrome.

## Nevirapine

### ***Clinical Trials in Adults***

The most serious adverse reactions associated with nevirapine are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters,

oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see **BOXED WARNING AND WARNINGS AND PRECAUTIONS**).

### ***Hepatic Reaction***

In controlled clinical trials, symptomatic hepatic events, regardless of severity, occurred in 4.0% (range: 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm<sup>3</sup> in women and >400 cells/mm<sup>3</sup> in men) place patients at increased risk of these events (see **WARNINGS AND PRECAUTIONS**).

Asymptomatic transaminase elevations (AST or ALT >5X ULN) were observed in 5.8% (range: 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in patients receiving nevirapine than in controls (see Table 6).

### ***Skin Reaction***

The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening (see **WARNINGS AND PRECAUTIONS**). Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine-associated rash (see **BOXED WARNINGS; WARNINGS AND PRECAUTIONS**).

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

Treatment-related adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 6.

### **Table 6: Percentage of Patients with Moderate or Severe Drug-Related Events in Adult Placebo-Controlled Trials**

	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

<sup>1</sup> Background therapy included 3TC for all patients and combinations of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). Patients had CD4<sup>+</sup> cell counts <200 cells/mm<sup>3</sup>.

<sup>2</sup> Background therapy included ZDV and ZDV + ddI; nevirapine monotherapy was administered in some patients. Patients had CD4<sup>+</sup> cell counts ≥200 cells/mm<sup>3</sup>.

**Laboratory Abnormalities:** Liver enzymes test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 4). Asymptomatic elevations in GGT occur frequently, but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (see Table 7).

**Table 7: Percentage of Adult Patients with Laboratory Abnormalities**

Laboratory Abnormality	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
<b>Blood Chemistry</b>				
SGPT (ALT) >250 U/L	5.3	4.4	14.0	4.0
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5

<b>Hematology</b>				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm <sup>3</sup>	1.3	1.0	0.4	1.5
Neutrophils <750/mm <sup>3</sup>	13.3	13.5	3.6	1.0

<sup>1</sup> Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4<sup>+</sup> cell counts <200 cells/mm<sup>3</sup>.

<sup>2</sup> Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some patients. Patients had CD4<sup>+</sup> cell counts ≥200 cells/mm<sup>3</sup>.

### **Observed During Clinical Practice:**

In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

***Body as a Whole:*** Fever, somnolence, drug withdrawal (see **DRUG INTERACTIONS**), redistribution/ accumulation of body fat (see **WARNINGS AND PRECAUTIONS**).

***Gastrointestinal:*** Vomiting

***Liver and Biliary:*** Jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure.

***Hematology:*** Anemia, eosinophilia, neutropenia.

***Musculoskeletal:*** Arthralgia, rhabdomyolysis associated with skin and/or liver reactions.

***Neurologic:*** Paresthesia

***Skin and Appendages:*** Allergic reactions, including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash-

associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see **WARNINGS AND PRECAUTIONS**), plus one or more of the following: Hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

In postmarketing surveillance, anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.

### **OVERDOSAGE**

There is no known antidote for **DUOVIR-N** Tablet.

#### **Lamivudine**

One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

#### **Zidovudine**

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposure up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and one report of grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3'-azido-3'-deoxy-5'-O-β-D glucopyranuronosythymidine (GZDV), is enhanced.

#### **Nevirapine**

There is no known antidote for nevirapine overdose. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced adverse events, including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, and weight decrease. All events subsided following discontinuation of nevirapine.

### **PACKAGING INFORMATION**

**DUOVIR-N Tablet**.....Container of 60 tablet

*Last updated: October 2010*