

Triomune 30/40

**Nevirapine 200 mg and stavudine 30mg/40mg and lamivudine 150mg
Tablets**

WARNING

TRIOMUNE IS NOT INTENDED FOR USE IN PATIENTS WHO ARE JUST INITIATING THERAPY WITH NEVIRAPINE. TRIOMUNE SHOULD BE ADMINISTERED ONLY TO PATIENTS WHO HAVE RECEIVED STAVUDINE + LAMVIUDINE (STANDARD DOSES) + NEVIRAPINE (200 MG OD) FOR 2 WEEKS AND HAVE DEMONSTRATED ADEQUATE TOLERABILITY TO NEVIRAPINE (SEE INDICATIONS, DOSAGE AND ADMINISTRATION).

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 COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4 COUNTS >250 CELLS/MM3, INCLUDING PREGNANT WOMEN RECEIVING NEVIRAPINE IN COMBINATION WITH OTHER ANTIRETROVIRALS FOR THE TREATMENT OF HIV INFECTION, ARE AT THE GREATEST RISK. HOWEVER, HEPATOTOXICITY ASSOCIATED WITH NEVIRAPINE USE CAN OCCUR IN BOTH GENDERS, ALL CD4 COUNTS AND AT ANY TIME DURING TREATMENT. 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 AS SOON AS POSSIBLE (SEE WARNINGS AND PRECAUTIONS).

IT IS ESSENTIAL THAT PATIENTS 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 TRIOMUNE FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT. IN ADDITION, THE 14-DAY LEAD-IN PERIOD WITH NEVIRAPINE 200 MG DAILY DOSING MUST BE STRICTLY FOLLOWED (SEE WARNINGS AND PRECAUTIONS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION INCLUDING LAMIVUDINE AND STAVUDINE (SEE WARNINGS AND PRECAUTIONS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION INCLUDING LAMIVUDINE AND STAVUDINE (SEE WARNINGS AND PRECAUTIONS).

**COMPOSITION
TRIOMUNE-30**

Each tablet contains
Stavudine 30 mg
Lamivudine 150 mg

Nevirapine 200 mg

TRIOMUNE – 40

Each tablet contains

Stavudine 40 mg

Lamivudine 150 mg

Nevirapine 200 mg

DESCRIPTION

TRIOMUNE is a combination of three drugs commonly used in the management of Human Immunodeficiency Virus (HIV) infection. Both stavudine 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 of HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor. It acts by directly inhibiting reverse transcriptase.

Each tablet of **TRIOMUNE** contains half of the commonly prescribed daily doses of stavudine, lamivudine and nevirapine. 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: Lamivudine is a synthetic nucleoside analogue. 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 HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. 3TC -TP is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.

Stavudine: Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate ($K_i = 0.0083$ to $0.032 \mu\text{M}$), and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3`-OH group. Stavudine triphosphate inhibits cellular DNA polymerases beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

Nevirapine: Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (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

Lamivudine:

Absorption and bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean \pm SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV - 1 -positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Effects of Food on Oral Absorption:

An investigational 25-mg dosage form of lamivudine administered orally to 12 asymptomatic, HIV - 1 -infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max} : 3.2 ± 1.3 hours) compared with the fasted state (T_{max} : 0.9 ± 0.3 hours); C_{max} in the fed state was $40\% \pm 23\%$ (mean \pm SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_{0-∞}) in the fed and fasted states; therefore, lamivudine Tablets and Oral Solution may be administered with or without food.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of

concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, $5.2\% \pm 1.4\%$ (mean \pm SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean \pm SD). In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean \pm SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg. **Stavudine:** Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The oral bioavailability of stavudine is $86.4 \pm 18.2\%$. Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 μ g/mL. Stavudine distributes equally between red blood cells and plasma. The metabolism of stavudine has not been elucidated in humans. Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

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 ± 0.4 μ g/mL (7.5 μ 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 ± 1.9 μ g/mL (17 ± 7 μ 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 (AUC_T) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. **NEVIMUNE** may be administered with or without food, antacid or didanosine.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was 1.21 ± 0.09 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 ^{14}C -nevirapine, approximately $91.4 \pm 10.5\%$ of the radiolabeled dose was recovered, with urine ($81.3 \pm 11.1\%$) representing the primary route of excretion compared to feces ($10.1 \pm 1.5\%$). 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 2 fold 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

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

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

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, **TRIOMUNE** should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk (see **WARNINGS AND PRECAUTIONS**).
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- The 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see **WARNINGS; 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 at which point an alternative regimen should be sought.

DOSAGE AND ADMINISTRATION

Adults

TRIOMUNE – 30

1 tablet twice daily for patients weighing < 60 kg

TRIOMUNE – 40

1 tablet twice daily for patients weighing ≥ 60 kg

TRIOMUNE 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 is recommended. Following this lead-in dose, a dose escalation (maintenance dose) to 200 mg nevirapine b.d 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 two 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 it is a fixed-dose tablet, **TRIOMUNE** should not be prescribed for patients requiring dosage adjustment or those experiencing dose-limiting adverse events.

Lamivudine

Because it is a fixed-dose combination, **TRIOMUNE** should not be prescribed for patients requiring dosage adjustment, such as if creatinine clearance < 50 mL/min.

Stavudine

Peripheral neuropathy: Patients should be monitored for the development of peripheral neuropathy, which is usually characterised by numbness, tingling, or pain in the feet or hands. If these symptoms develop during treatment, **TRIOMUNE** therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose.

If peripheral neuropathy recurs after resumption of **TRIOMUNE**, permanent discontinuation of **TRIOMUNE** should be considered.

Since **TRIOMUNE** is a fixed-dose combination, it cannot be used under these circumstances.

Nevirapine

TRIOMUNE should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see **WARNINGS AND**

PRECAUTIONS). Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased or start therapy with **TRIOMUNE** until the rash has resolved (see **WARNINGS AND PRECAUTIONS**). If rash persists beyond the 14 day lead-in period, do not dose escalate to **TRIOMUNE** twice daily. The **TRIOMUNE** once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought.

If clinical hepatitis occurs, nevirapine should be permanently discontinued and not restarted after recovery.

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

CONTRAINDICATIONS

TRIOMUNE is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the formulation.

TRIOMUNE is contraindicated in patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment [**see WARNINGS AND PRECAUTIONS**].

TRIOMUNE is also contraindicated in 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.d. (see **INDICATIONS**).

The 14-day lead-in period with **TRIOMUNE** daily dosing has been demonstrated to reduce the frequency of rash [**see WARNINGS AND PRECAUTIONS**].

If rash persists beyond the 14 day lead-in period, do not dose escalate to **TRIOMUNE** twice daily. The 200 mg nevirapine once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought.

WARNINGS AND PRECAUTIONS

When administering **TRIOMUNE**, the complete product information for each

therapeutic component should be consulted before initiation of treatment.

Nevirapine

General: 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 two 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.

Skin Reactions: Severe, 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. 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, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from nevirapine.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation and administration of **TRIOMUNE** should not occur until the rash has resolved (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 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.

Hepatic Events

Lamivudine and stavudine

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and lamivudine. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering lamivudine or stavudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Treatment with **TRIOMUNE** should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness) might be indicative of development of symptomatic hyperlactatemia or lactic acidosis syndrome.

The safety and efficacy of stavudine have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events,

and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Use with Didanosine and Hydroxyurea-Based Regimens

An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. This combination should be avoided.

Nevirapine

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 hyperbilirubinaemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver function 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,

or alternative diagnoses are possible

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, **TRIOMUNE** should be permanently discontinued. Do not restart **TRIOMUNE** 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 threefold 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/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm³ (6.3% versus 1.2% for men with CD4 counts <400 cells/mm³). However, all patients, regardless of gender, CD4 count, 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 is associated with a greater risk of later symptomatic events (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.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, **TRIOMUNE** should not be administered to patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment.

Neurologic Symptoms

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling or pain in the hands

or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy or concurrent neurotoxic therapy.

Pancreatitis

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

Post-treatment Exacerbations of Hepatitis

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, 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 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 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV 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 post treatment exacerbations of hepatitis.

Patients with HIV and Hepatitis B Virus Co-infection

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV.

In non-HIV-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-infected patients who have received lamivudine-containing antiretroviral regimens in presence of concurrent infection with hepatitis B virus. Post-treatment exacerbations of hepatitis have also been reported.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co administered with lamivudine in HIV/HCV co-infected patients, **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine 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 (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine, stavudine 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 lump), 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.

Others

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving nevirapine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Drug Interactions

Stavudine: Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine is not recommended. *In vitro* data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of these *in vitro* interactions is unknown; therefore concomitant use of stavudine with either of these drugs should be undertaken with caution.

Lamivudine :

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

No data are available regarding interactions with other drugs-that have renal clearance mechanisms similar- to that of lamivudine.

Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., 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**)

Zalcitabine:

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.

Therefore, use of lamivudine in combination with zalcitabine is not recommended.

Trimethoprim/Sulfamethoxazole (TMP/SMX)

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.

Drugs with No Observed Interactions With lamivudine:

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

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 coadministered with nevirapine.

Clinical comments about possible dosage modifications based on observed pharmacokinetic changes are listed in Table 1. 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 listed in Table 2. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the 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.

St. John`s wort: Concomitant use of St. John`s wort (*hypericum perforatum*) or St. John`s wort- containing products and nevirapine is not recommended. Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John`s wort 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.

Table 1. Established Drug Interactions: Alteration in Dose or Regimen may be recommended based on drug interaction studies

Drug name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical comment
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	Appropriate doses for this combination are not established.
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.
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>Lopinavir/ritonavir 400/100 mg tablets can be used twice-daily in combination with nevirapine</p> <p>with no dose adjustment in antiretroviral naïve patients.</p> <p>A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with nevirapine in treatment experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or</p>

		<p>laboratory evidence).</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, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to < 15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those > 45 kg twice daily when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.</p>
Methadone	↓Methadone	<p>Methadone levels may be 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 methadone dose should be adjusted accordingly.</p>
Nelfinavir	↓Nelfinavir M8 Metabolite	<p>The appropriate dose for nelfinavir in combination</p>

	↓Nelfinavir C _{min}	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	↓Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

Table 2. Potential drug Interactions: Use with caution, dose adjustment of co-administered Drug may be needed due to possible decrease in Clinical Effect

Examples of Drugs in which plasma concentrations may be decreased by Co-administration with Nevirapine	
Drug class	Examples of Drugs
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Renal Impairment

The dose of both lamivudine and stavudine should be reduced for patients with CrCL <50 mL/min. For nevirapine, dose reduction is required when CrCL <20 mL/min. Additional doses of nevirapine are required for patients on dialysis. Since **TRIOMUNE** is a fixed-dose combination, it should not be prescribed for these patient populations.

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.

Stavudine pharmacokinetics was not altered in 5 non-HIV infected patients

with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

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.

Pregnancy

Lamivudine and stavudine are classified under category C whereas nevirapine is classified under category B. There are no adequate and well-controlled studies in pregnant women. **TRIOMUNE** should be used during pregnancy only if the potential benefits outweigh the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in non pregnant individuals receiving nucleoside analogues. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk. Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV infection. Regardless of pregnancy status, women with CD4 counts >250 cells/mm³ should not initiate **TRIOMUNE** unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women.

Lactation

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV infection. It is not known whether stavudine is excreted in human milk. Lamivudine and nevirapine is present in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed to discontinue nursing if they are receiving **TRIOMUNE**.

Pediatrics

TRIOMUNE is not intended for use in pediatric patients.

UNDESIRABLE EFFECTS

Lamivudine

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.

The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1infected patients in 7 clinical trials. The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough. Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg three times daily for upto 24 weeks are listed below.

Table 3. Selected Clinical Adverse Events ($\geq 5\%$ Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	Lamivudine 150 mg twice daily plus Zidovudine (n = 251)	Zidovudine* (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea and vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		

Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs and symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

* Either zidovudine monotherapy or zidovudine in combination with zalcitabine

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 4.

Table 4. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	Lamivudine plus zidovudine	Zidovudine [†]	Lamivudine plus current therapy	Placebo plus current therapy [‡]
Absolute neutrophil count	7.2%	5.4%	15%	13%

(<750/mm ³)				
Hemoglobin (< 8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (< 50,000/mm ³)	0.4%	1.3%	2.8%	3.8%
ALT (> 5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (> 2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (> 2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

*The median duration on study was 12 months.

† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

‡ Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see **WARNINGS AND PRECAUTIONS: Pregnancy**), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily were similar. **Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. 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.

Body as a Whole: Redistribution/accumulation of body fat

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycaemia.

General: Weakness.

Haemic and Lymphatic: Anaemia (including pure red cell aplasia and severe anaemias progressing on therapy), lymphadenopathy, splenomegaly.

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

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

Stavudine

Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently

in patients being treated with neurotoxic drug therapy, including didanosine, in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half of the dose. If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone.

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study included headache, diarrhea, peripheral neurologic symptoms/neuropathy, rash, nausea and vomiting. Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Laboratory Abnormalities: Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 5.

Table 5: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)

Parameter	Percent (%)			
	START 1		START 2	
	stavudine + lamivudine + indinavir (n=100)	Zidovudine + lamivudine + indinavir (n=102)	stavudine + didanosine + indinavir (n=102)	zidovudine + lamivudine + indinavir (n=103)
Bilirubin (≥ 2.6 x ULN)	7	6	16	8
SGOT (AST) (≥ 5 x ULN)	5	2	7	7
SGPT (ALT) (≥ 5 x ULN)	6	2	8	5
GGT (≥ 5 x ULN)	2	2	5	2
Lipase (≥ 2 x ULN)	6	3	5	5
Amylase (≥ 2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

Observed during clinical practice: The following events have been identified during post-approval use of stavudine. 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 their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

Body as a Whole: Abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat.

Digestive Disorders: Anorexia

Exocrine Gland Disorders: Pancreatitis (including fatal cases)

Haematologic Disorders: Anaemia, leucopenia and thrombocytopenia

Liver: Symptomatic hyperlactatemia/Lactic acidosis and hepatic steatosis, hepatitis and liver failure

Musculoskeletal: Myalgia

Nervous system: Insomnia, severe motor weakness (most often reported in the setting of lactic acidosis).

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 oedema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see **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/mm³ in women and >400 cells/mm³ 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 clinically 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, 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.

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 ¹		Trials 1037, 1038, 1046 ²	
	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

¹Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts < 200 cells/mm³

²Background therapy included ZDV and ZDV + ddI, Nevirapine monotherapy was administered in some patients. Patients had CD4+cell count ≥ 200 cells/mm³

Laboratory Abnormalities: Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 5). 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

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Blood chemistry				
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
Hematology				
Hemoglobin < 8.0 g/dL	3.2	4.1	0	0

Platelets <50,000/mm ³	1.3	1.0	0.4	1.5
Neutrophils < 750/mm ³	13.3	13.5	3.6	1.0

¹ Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts < 200 cells/mm³

² Background therapy included ZDV and ZDV+ddI; Nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥ 200 cells/mm²

Post Marketing Surveillance: The following events have been reported with the use of nevirapine in clinical practice:

Body as a whole: fever, somnolence, drug withdrawal, redistribution/accumulation of body fat

Gastrointestinal: vomiting

Liver and Biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure

Haematology: anaemia, eosinophilia, neutropenia

Musculoskeletal: arthralgia

Neurologic: paraesthesia

Skin and Appendages: allergic reactions including anaphylaxis, angio-oedema, 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 oedema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

OVERDOSAGE

Lamivudine

There is no known antidote for lamivudine. It is not known whether lamivudine can be removed by peritoneal dialysis or haemodialysis. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as

required.

Stavudine

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by haemodialysis; the mean + SD haemodialysis clearance of stavudine is 120 + 18 ml/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

Nevirapine

There is no known antidote for nevirapine overdosage. 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 events including oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting and weight decrease. All events subsided following discontinuation of nevirapine.

PACKAGING INFORMATION

TRIOMUNE – 30 Container of 30 tablets

TRIOMUNE – 40 Container of 30 tablets

Last updated: May 2009