

Stavudine 6 mg/12 mg, Lamivudine 30 mg/60 mg and Nevirapine 50 mg/100 mg
Tablets

TRIOMUNE BABY/JUNIOR

WARNING

LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY AND SKIN REACTIONS:

TRIOMUNE BABY/JUNIOR TABLETS ARE NOT INTENDED FOR USE IN PATIENTS WHO ARE JUST INITIATING THERAPY WITH NEVIRAPINE. TRIOMUNE BABY/JUNIOR TABLETS SHOULD BE ADMINISTERED ONLY TO PATIENTS WHO HAVE RECEIVED STAVUDINE PLUS LAMIVUDINE TWICE DAILY PLUS NEVIRAPINE ONCE DAILY FOR 2 WEEKS AND HAVE DEMONSTRATED ADEQUATE TOLERABILITY TO NEVIRAPINE (SEE INDICATIONS; DOSAGE AND ADMINISTRATION).

HEPATOTOXICITY:

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⁺ CELL COUNTS AT INITIATION OF THERAPY PLACE PATIENTS AT INCREASED RISK; WOMEN WITH CD4⁺ CELL COUNTS >250 CELLS/MM³, 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⁺ 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 TRIOMUNE BABY/JUNIOR FOR OCCUPATIONAL AND NON-OCCUPATIONAL 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 TRIOMUNE BABY/JUNIOR TABLETS AND SEEK MEDICAL EVALUATION IMMEDIATELY (SEE WARNINGS AND PRECAUTIONS).

SKIN REACTIONS:

SEVERE, LIFE-THREATENING SKIN REACTIONS, INCLUDING FATAL CASES, HAVE OCCURRED IN PATIENTS TREATED WITH NEVIRAPINE. THESE HAVE

HYPERSENSITIVITY REACTIONS MUST DISCONTINUE TRIOMUNE BABY/JUNIOR TABLETS 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 VIRAMUNE 200 MG DAILY DOSING HAS BEEN OBSERVED TO DECREASE THE INCIDENCE OF RASH AND MUST BE FOLLOWED (SEE WARNINGS AND PRECAUTIONS).

MONITORING:

PATIENTS MUST BE MONITORED INTENSIVELY DURING THE FIRST 18 WEEKS OF THERAPY WITH TRIOMUNE BABY/JUNIOR TABLETS 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 BABY/JUNIOR TABLETS FOLLOWING SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT.

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

FATAL AND NON-FATAL PANCREATITIS HAS OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE IN BOTH TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF

COMPOSITION

TRIOMUNE BABY Tablets

Each tablet contains:

Stavudine 6 mg

Lamivudine 30 mg

Nevirapine 50 mg

TRIOMUNE JUNIOR Tablets

Each tablet contains:

Stavudine 12 mg

Lamivudine 60 mg

Nevirapine 100 mg

DOSAGE FORM

Oral, dispersible fixed-dose tablet

DESCRIPTION

Each tablet of **TRIOMUNE BABY/JUNIOR** contains stavudine, lamivudine and nevirapine. These three drugs are commonly used in the management of the human immunodeficiency virus (HIV) infection. Both stavudine and lamivudine belong to the nucleoside analog 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 (NNRTI). It acts by directly inhibiting reverse transcriptase.

PHARMACOLOGY

Pharmacodynamics

Nevirapine

Nevirapine is a NNRTI of HIV-1. Nevirapine binds directly to reverse transcriptase 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.

Stavudine

Stavudine, a nucleoside analog of thymidine, is phosphorylated by cellular kinases to the active metabolite, stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate, thymidine triphosphate ($K_i = 0.0083$ to $0.032 \mu\text{M}$) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases, beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

Lamivudine

Lamivudine is a synthetic nucleoside analog. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase via DNA chain termination after incorporation of the nucleotide analog into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases, alpha, beta and gamma.

Pharmacokinetics

The pharmacokinetics of nevirapine, stavudine and lamivudine was determined in Zambian children who received lamivudine, stavudine and nevirapine dispersible tablets (60 mg/12 mg/100 mg) and (30 mg/6 mg/50 mg).*

A total of 64 children aged <3 years (n=16), 3 to 6 years (n=19), 7 to 10 years (n=17) and 11 to 14 years (n=12) were dosed according to body weight. The children received doses similar to those listed in the **DOSAGE and ADMINISTRATION** section, except

for a few children who received a lead-in dosing with this formulation and a few children in the lowest weight bands who received a somewhat different dosing. At least 4 weeks after starting lamivudine, stavudine and nevirapine dispersible tablets (60 mg/12 mg/100 mg) and (30 mg/6mg/50 mg), a 12-hour pharmacokinetic curve was recorded after observed intake. Table 1 summarizes the pharmacokinetic parameters in the children.

Table 1: Pharmacokinetic parameters in pediatric subjects following administration of lamivudine/stavudine/nevirapine dispersible tablets

	Mean \pm SD	Range
Lamivudine		
C _{min} (mg/L)	0.09	<0.05, 0.20
C _{max} (mg/L)	1.32 \pm 0.68	0.20, 3.42
AUC ₁₂ (mg*hr/L)	5.36 \pm 2.27	1.59, 11.45
Stavudine		
C _{min} (mg/L)	<0.15	<0.15, 0.03
C _{max} (mg/L)	0.44 \pm 0.16	0.09, 0.89
AUC ₁₂ (mg*hr/L)	1.02 \pm 0.39	0.35, 2.16
Nevirapine		
C _{min} (mg/L)	6.0 \pm 2.9	1.4, 16.9
C _{max} (mg/L)	9.9 \pm 3.6	3.8, 22.5
AUC ₁₂ (mg*hr/L)	94.2 \pm 37.7	32.1, 232

Nevirapine plasma concentrations were higher than those previously reported in adults and children taking other formulations of nevirapine at recommended doses, while plasma concentrations of stavudine and lamivudine were comparable to those previously reported in adults and children taking other formulations of stavudine and lamivudine at recommended doses.

INDICATIONS

TRIOMUNE BABY/JUNIOR Tablets are indicated for the treatment of HIV-1 infection in children less than 30 kg, once patients have demonstrated adequate tolerability to nevirapine during the lead-in dosing period (see **DOSAGE AND ADMINISTRATION**).

- The 14-day lead-in period with nevirapine once daily dosing has been demonstrated to reduce the frequency of rash (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).
- If rash persists beyond the 14 day lead-in period, do not dose escalate to **TRIOMUNE BABY/JUNIOR Tablets** twice daily. The lead-in dosing regimen should not be continued beyond 28 days, at which point an alternative regimen should be sought.

DOSAGE AND ADMINISTRATION

Lead-in Dosing

TRIOMUNE BABY/JUNIOR Tablets are a fixed-dose combination, and cannot be used during the 2-week period of nevirapine lead-in therapy.

Chronic Dosing

Following this lead-in dose, treatment with **TRIOMUNE BABY/JUNIOR Tablets** or **Triomune-30** tablets (based on the weight of the child) twice daily may be carried out in the absence of any hypersensitivity reactions (e.g., rash, liver function test abnormalities; see **WARNINGS AND PRECAUTIONS**). Table 2 lists the dosage schedule for **TRIOMUNE BABY/JUNIOR Tablets** twice daily.

Table 2: Chronic dosage schedule for TRIOMUNE BABY/JUNIOR Tablets

Weight Range	Schedule
3 to <6 kg	1 tablet TRIOMUNE BABY b.i.d.
6 to <10 kg	1½ tablets TRIOMUNE BABY b.i.d.
10 to <15 kg	1 tablet TRIOMUNE JUNIOR b.i.d.
15 to <20 kg	1 tablet TRIOMUNE JUNIOR in the morning and 1½ tablets TRIOMUNE JUNIOR in the evening
20 to <25 kg	1½ tablets TRIOMUNE JUNIOR b.i.d.
25 to <30 kg	2 tablets TRIOMUNE JUNIOR b.i.d.

For Children ≥30 kg

For children with higher body weights, **Triomune-30** tablets twice daily may be used, as per the schedule given below in Table 5.

Table 3: Continuous dosage schedule for Triomune-30 tablets

Weight Range	Schedule
≥30 kg	1 tablet Triomune-30 b.i.d.

Method of Preparation

For children unable to swallow tablets, disperse one tablet in two teaspoonfuls (10 ml) of drinking water and administer. The dispersion should be drunk immediately and is palatable with a bland taste.

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 **TRIOMUNE BABY/JUNIOR Tablets**. 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.

Stavudine

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling or pain in the feet or hands. These symptoms may be difficult to detect in young children. If these symptoms develop during treatment, stavudine 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.

Nevirapine

Intensive clinical and laboratory monitoring, including liver enzyme 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 enzyme 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 **TRIOMUNE BABY/JUNIOR** treatment (see **WARNINGS AND PRECAUTIONS**). In some cases, hepatic injury has progressed despite discontinuation of treatment.

CONTRAINDICATIONS

TRIOMUNE BABY/JUNIOR Tablets are contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the formulation.

TRIOMUNE BABY/JUNIOR Tablets are also contraindicated in patients who are just initiating therapy with nevirapine. These patients require a lead-in-dose of nevirapine o.d. (see **INDICATIONS**).

TRIOMUNE BABY/JUNIOR Tablets are contraindicated in patients with moderate or severe (Childs Pugh Class B or C, respectively) hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Post-Exposure Prophylaxis

TRIOMUNE BABY/JUNIOR Tablets are contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

When administering **TRIOMUNE BABY/JUNIOR Tablets**, 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 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 has been demonstrated to reduce the frequency of rash.

Skin Reactions: Severe, life-threatening skin reactions, including fatal cases, have been reported, 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 **TRIOMUNE BABY/JUNIOR Tablets** and seek medical evaluation immediately. Do not restart **TRIOMUNE BABY/JUNIOR Tablets** following severe 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 **TRIOMUNE BABY/JUNIOR Tablets**.

TRIOMUNE BABY/JUNIOR Tablets must be initiated with a once daily, 14-day lead-in period, which has been shown to reduce the frequency of rash. **TRIOMUNE BABY/JUNIOR Tablets** 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 should not shift to a twice daily, maintenance dose of **TRIOMUNE BABY/JUNIOR Tablets** 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 treatment with **TRIOMUNE BABY/JUNIOR Tablets** 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.

Hepatic Events

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 the 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 the controls, through the 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. Some of these events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, 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 **TRIOMUNE BABY/JUNIOR Tablets** 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 (see BOXED WARNINGS; DOSAGE AND ADMINISTRATION).

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, **TRIOMUNE BABY/JUNIOR Tablets** should be permanently discontinued. Do not restart **TRIOMUNE BABY/JUNIOR Tablets** 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 females with high CD4 cell counts. In general, during the first 6 weeks of treatment, females have a threefold higher risk than males for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, females with CD4 cell counts >250

cells/mm³ had a 12-fold higher risk of symptomatic hepatic adverse events compared to those with CD4 cell counts <250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in males with CD4 cell counts >400 cells/mm³ (6.3% versus 1.2% for males with CD4 cell counts <400 cells/mm³). However, all patients, regardless of gender, CD4 cell count or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 cell counts. 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.

In addition, serious hepatotoxicity (including liver failure requiring a transplant 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 trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, patients with either hepatic fibrosis or cirrhosis should be monitored carefully for evidence of drug-induced toxicity. **TRIOMUNE BABY/JUNIOR Tablets** should not be administered to patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (see **CONTRAINDICATIONS**).

Lamivudine and Stavudine

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination, including lamivudine and stavudine. 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. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. 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.

Particular caution should be exercised when administering lamivudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. 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 lactic acidosis development.

Treatment with lamivudine 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).

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 pre-existing 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.

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.

Caregivers of young children receiving stavudine therapy should be instructed regarding the detection and reporting of peripheral neuropathy.

Pancreatitis

Fatal and non-fatal pancreatitis has 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 the 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. In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

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 has been seen 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 postmarketing 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.

Important Differences among Lamivudine-Containing Products

TRIUMUNE BABY/JUNIOR Tablets have been developed for children with HIV/AIDS. **Lamivir-HBV** tablets are for adult patients with chronic hepatitis B, whereas **LAMIVIR** oral solution is for children and **LAMIVIR** tablets are for adults with HIV/AIDS.

Lamivudine tablets and oral solution contain a higher dose of lamivudine than **Lamivir-HBV** tablets.

Lamivudine has not been adequately studied for the treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with lamivudine is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid

emergence of HIV-1 resistance is likely to result because of the sub-therapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients dually infected with HIV-1 and HBV, lamivudine should be used as part of an appropriate combination regimen.

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 HBV 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 HBV.

Use with Other Lamivudine- and Emtricitabine-Containing Products

Lamivudine should not be administered concomitantly with other lamivudine-containing products.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogs such as lamivudine and stavudine. 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 and interferon alfa with or without ribavirin.** Patients receiving interferon alpha 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, any patient 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, the 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, the use of lamivudine in combination with zalcitabine is not recommended.

Trimethoprim/Sulfamethoxazole (TMP/SMX): No change in the 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 (CY) 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 observed pharmacokinetic changes are listed in Table 5. 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 CYP450 system. These potential drug interactions are listed in Table 6. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 6, 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 NNRTIs, including nevirapine, with St. John's wort is expected to substantially

decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine, leading to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs.

Table 4: 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
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 the 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.
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</p>

		<p>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 twice daily.</p> <p>Refer to the lopinavir/ritonavir package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine.</p>
Methadone	↓ Methadone	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.
Nelfinavir	<p>↓ Nelfinavir M8 metabolite</p> <p>↓ Nelfinavir C_{min}</p>	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	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.
Potential Drug Interactions		
Drug Class	Examples of Drugs	
Anti-arrhythmics	Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma concentrations may be decreased.
Antifungals	Itraconazole	Plasma concentrations of some azole antifungals may be decreased. Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations.
Calcium channel blockers	Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.
Cancer chemotherapy	Cyclophosphamide	Plasma concentrations may be decreased.
Ergot alkaloids	Ergotamine	Plasma concentrations may be decreased.
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.
Motility agents	Cisapride	Plasma concentrations may be decreased.
Opiate agonists	Fentanyl	Plasma concentrations may be decreased.
Antithrombotics	Warfarin	Plasma concentrations may be increased. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Use in Specific Populations

Renal Impairment

Since urinary excretion is a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in those with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of stavudine in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Although there are insufficient data to recommend a specific dose adjustment of lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or increase in the dosing interval should be considered.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidneys. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with creatinine clearance (CrCL) ≥ 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated (see **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGY**). Since **TRIOMUNE BABY/JUNIOR Tablets** are a fixed-dose combination, they 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.

Because 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.

UNDESIRABLE EFFECTS

Lamivudine

Pediatric Patients

Selected clinical adverse events and physical findings with a $\geq 5\%$ frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m² three times

daily compared with didanosine in therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

Table 5: Selected clinical adverse events and physical findings (≥5% frequency) in pediatric patients in Study ACTG300

Adverse Reaction	Lamivudine plus Zidovudine (n=236)	Didanosine (n=235)
Body as a Whole Fever	25%	32%
Digestive Hepatomegaly Nausea and vomiting Diarrhea Stomatitis Splénomegaly	11% 8% 8% 6% 5%	11% 7% 6% 12% 8%
Respiratory Cough Abnormal breath sounds/wheezing	15% 7%	18% 9%
Ear, Nose and Throat Signs or symptoms of the ears* Nasal discharge or congestion	7% 8%	6% 11%
Other Skin rashes Lymphadenopathy	12% 9%	14% 11%

* Includes pain, discharge, erythema, or swelling of an ear

Selected laboratory abnormalities experienced by therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6: Frequencies of selected laboratory abnormalities in pediatric patients in Study ACTG300

Test (Threshold Level)	Lamivudine Plus Zidovudine	Didanosine
Absolute neutrophil count	8%	3%

(<400/mm ³)		
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm ³)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Of these, 3 patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Limited short-term safety information is available from two small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at week 38 or 36 of gestation. Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other non-fatal gastroenteritis or diarrhea cases were reported, including 1 infant with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups further limits assessments of causality, but it should be assumed that perinatally-exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of *in utero* and infant lamivudine exposure are not known.

Observed During Clinical Practice

In addition to the adverse events reported from clinical trials, the events given below 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 (see **WARNINGS AND PRECAUTIONS, Fat Redistribution**).

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemia 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: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

Stavudine

Pediatric Patients

Adverse events and laboratory abnormalities reported to occur in pediatric patients in clinical studies were generally consistent with the safety profile of stavudine in adults. These studies include ACTG 240, where 105 pediatric patients, aged 3 months to 6 years, received stavudine 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received stavudine 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received stavudine 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

Adults

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 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.

Observed During Clinical Practice

The events given below 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 cases).

Hematologic Disorders: Anemia, leukopenia, thrombocytopenia and macrocytosis.

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

Pediatric Patients

Adverse events were assessed in the BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of nevirapine (n=305) in which pediatric patients received combination treatment with nevirapine. In this trial, 2 patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome.

Safety was also assessed in the BI Trial 1100.882 (ACTG 180), an open-label trial of nevirapine (n=37) in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in the BI Trial 1100.892). The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of nevirapine was also examined in the BI Trial 1100.1368, an open-label, randomized clinical study performed in South Africa in which 123 HIV-1 infected treatment-naïve patients between 3 months and 16 years of age received combination treatment with nevirapine oral suspension, lamivudine and zidovudine for 48 weeks. Rash (all causality) was reported in 21% of the patients, 4 (3%) of whom discontinued the drug due to rash. All 4 patients experienced the rash early in the course of therapy (<4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (8.9%), anemia (7.3%) and hepatotoxicity (2.4%).

Safety information on the use of nevirapine in combination therapy in pediatric patients, 2 weeks to <3 months of age, was assessed in 36 patients from the BI Trial 1100.1222 (PACTG 356) study. No unexpected safety findings were observed although granulocytopenia was reported more frequently in this age group compared to the older pediatric age groups and adults.

Postmarketing Surveillance

In addition to the adverse events identified during the clinical trials, the following events have been reported with the use of nevirapine in clinical practice.

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

Gastrointestinal: Vomiting.

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

Hematology: Anemia, eosinophilia, neutropenia.

Musculoskeletal: Arthralgia, rhabdomyolysis.

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 was more commonly observed in children although the development of anemia due to concomitant medication use cannot be ruled out.

OVERDOSAGE

Lamivudine

There is no known antidote for lamivudine. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

Stavudine

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic continuous overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis.

Nevirapine

There is no known antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg/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 the discontinuation of nevirapine.

PACKAGING INFORMATION

TRIOMUNE BABY Tablets.....Container of 60 tablets
TRIOMUNE JUNIOR Tablets.....Container of 60 tablets

Last updated: November 2010