

PRODUCT MONOGRAPH

^{Pr}Apo-TriAvir

zidovudine, lamivudine and nevirapine

300 mg zidovudine, 150 mg of lamivudine and 200 mg nevirapine tablets

Antiretroviral Agent

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Pr Apo-TriAvir
300 mg zidovudine, 150 mg of lamivudine and 200 mg nevirapine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Oral tablet /300 mg zidovudine, 150 mg lamivudine, and 200 mg nevirapine	None. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Apo-TriAvir (zidovudine, lamivudine and nevirapine) is indicated for the treatment of HIV-1 infection in settings where more preferred therapies cannot be used.

Apo-TriAvir has not been evaluated in clinical trials. This indication is based on bioavailability studies. See **Part II, CLINICAL TRIALS, Comparative Bioavailability Studies**, pp 43-44.

The decision to use Apo-TriAvir should take into account liver and skin toxicity, potentially fatal, especially in patients with higher CD4 counts and in women, due to the nevirapine component (see **Warnings and Precautions**).

Clinical trials have not established the equivalence of nevirapine to protease inhibitors or other NNRTIs.

Based on serious and life-threatening hepatotoxicity observed with nevirapine in controlled and uncontrolled studies, Apo-TriAvir 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.

Geriatrics (>55 years of age):

Nevirapine has not been evaluated in patients beyond the age of 55 years and Apo-TriAvir has not been evaluated in clinical trials.

Pediatrics (<15 years of age):

Safety and effectiveness of nevirapine in HIV-1 infected pediatric patients younger than 15 years of age has not been established. Nevirapine, one of the components of Apo-TriAvir, is metabolized more rapidly in pediatric patients than in adults. Apo-TriAvir has not been evaluated in clinical trials.

CONTRAINDICATIONS

Apo-TriAvir (zidovudine, lamivudine and nevirapine) is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product (for a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING**). The co-administration of Apo-TriAvir with lamivudine or zidovudine or nevirapine is not recommended, except in the lead-in dosing period (See **DOSAGE AND ADMINISTRATION**)

Due to the active ingredient zidovudine, Apo-TriAvir is contraindicated in patients with abnormally low neutrophil counts ($< 0.75 \times 10^9/L$) or abnormally low hemoglobin levels (< 75 g/L or 4.65 mmol/L)

Apo-TriAvir should not be administered to patients with severe hepatic dysfunction or pre-treatment AST or ALT $> 5X$ Upper Limit of Normality (ULN).

Apo-TriAvir should not be readministered to patients who have been discontinued for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

Apo-TriAvir should not be readministered in patients who previously had AST or ALT $> 5X$ Upper Limit of Normality (ULN) during nevirapine therapy (see **WARNINGS AND PRECAUTIONS** section).

WARNINGS AND PRECAUTIONS

Hepatotoxicity:

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. Female gender and higher CD4 counts at the initiation of therapy place patients at increased risk of hepatic adverse events. Increased AST or ALT levels and/or co-infection with hepatitis B and C at the start of antiretroviral therapy are associated with a greater risk of hepatic adverse events. (see **General and Hepatic/Biliary/Pancreatic sections** below.)

Skin Rash:

Severe, life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, occurring almost exclusively during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome characterized by rash, constitutional findings, and organ dysfunction (see **ADVERSE REACTIONS** section). Patients should be carefully monitored during the first 18 weeks of treatment. Nevirapine should not be restarted following severe skin rash or hypersensitivity reaction.

Lactic Acidosis and Severe Hepatomegaly with Steatosis:

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

been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with Apo-TriAvir 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 (See **General and Hepatic/Biliary/Pancreatic sections** below.)

Post-Treatment Exacerbation of Hepatitis B:

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Apo-TriAvir is not indicated for the treatment of chronic HBV infection and the safety and efficacy of Apo-TriAvir have not been established in patients co-infected with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Apo-TriAvir (see **Post-Treatment Exacerbation of Hepatitis B section** below).

General

Women and patients with higher CD4 counts are at increased risk of hepatic adverse events. The first 18 weeks of therapy with Apo-TriAvir 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, however it may be prudent to conduct clinical and laboratory monitoring more often than once per month; for example, 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 treatment. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy.

The incidence of adverse reactions appears to increase with disease progression and patients should be monitored carefully, especially as disease progression occurs. The complete prescribing information for all agents being considered for use with Apo-TriAvir (zidovudine, lamivudine and nevirapine) should be consulted before combination therapy with Apo-TriAvir is initiated.

Hepatic/Biliary/Pancreatic

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 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 the initiation of therapy place patients at greater risk of hepatic adverse events. Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies with nevirapine, Apo-TriAvir should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection, or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless the benefit outweighs

the risk. In some cases, hepatic injury has progressed despite discontinuation of therapy. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue Apo-TriAvir immediately and seek medical evaluation immediately. Apo-TriAvir or other nevirapine-containing antiretroviral products should not be restarted following severe hepatic, skin or hypersensitivity reactions.

In clinical trials, the risk of 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. Some of these events have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia. Rash and fever accompanied some of these hepatic events. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Increased AST or ALT levels and/or co-infection with hepatitis B and C at the start of antiretroviral therapy are associated with a greater risk of hepatic adverse events.

In general, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/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 also observed in men with CD4 counts >400 cells/mm³ (6.3% versus 2.3% for men with CD4 counts <400 cells/mm³).

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.

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment (see **WARNINGS AND PRECAUTIONS** section). Monitoring should continue at frequent intervals thereafter, depending on the patient's clinical status. Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained 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 hepatic injury should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible (see **WARNINGS AND PRECAUTIONS** section).

If clinical hepatitis occurs, nevirapine should be permanently discontinued and not restarted after recovery. If either AST or ALT increase to $>5X$ ULN, nevirapine should be immediately

stopped. nevirapine should not be readministered to patients who have been discontinued for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine (see **Guideline for the MANAGEMENT OF HEPATIC EVENTS**), in some cases hepatic injury progresses despite the discontinuation of treatment.

If AST or ALT is >2X ULN, liver tests should be monitored more frequently.

Asymptomatic elevation of liver enzymes occur frequently in patients infected with HIV and is not necessarily a contraindication to initiating therapy with nevirapine. Asymptomatic GGT elevations are not a contraindication to continuing therapy.

Nevirapine is extensively metabolised by the liver and nevirapine metabolites are eliminated largely by the kidney. Single dose pharmacokinetic results suggest caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction. Nevirapine should not be administered to patients with severe hepatic dysfunction (see **CONTRAINDICATIONS** section).

When administering nevirapine as part of a multi-drug antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

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. Nevirapine therapy has not been shown to reduce the risk of horizontal transmission of HIV-1 to others.

Management of Hepatic Events with Apo-TriAvir*

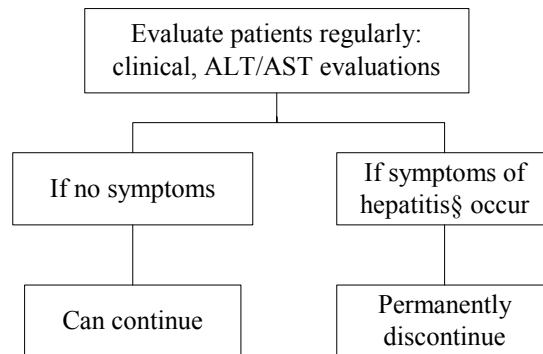
Risk Factors for Symptomatic Hepatic Events

- Elevated pretreatment ALT or AST
- HBV and /or HCV coinfection‡
- Higher CD4+ cell count at initiation of Apo-TriAvir therapy
- Female gender
- **Women with CD4+ cell counts greater than 250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of hepatotoxicity, including fatal events**

Patient Management

- Counsel patients that if signs or symptoms of hepatitis§, severe skin reactions, or hypersensitivity occur, then discontinue Apo-TriAvir and seek medical evaluation immediately
- Frequent clinical and laboratory monitoring is essential, especially during the first 18 weeks of treatment – extra vigilance is warranted during the first 6 weeks
- Baseline assessments should include LFTs and HBV/HCV status
- If hepatic symptoms occur:
 - Permanently discontinue Apo-TriAvir
 - Consider stopping all potential hepatotoxins, including concomitant antiretrovirals
 - Evaluate patients for other causes, including HBV/HCV coinfection, alcohol use, and coadministered medications
 - Continue to monitor patient until symptoms resolve
- In some cases, hepatic injury has progressed despite discontinuation of treatment

Hepatic Event Management



Other Important Information

- The 14-day lead –in period with nevirapine 200 mg daily must be strictly followed†
- Nevirapine should not be used for multiple-dose post-exposure prophylaxis. Serious hepatotoxicity, including hepatic failure, has occurred in this setting

* Hepatic events include symptomatic hepatitis and/or ALT/AST >5X ULN

‡ Risk factors associated with regimens and without nevirapine

§ Signs and symptoms

† If nevirapine has been interrupted for >7 days, reintroduce with 200 mg once daily lead-in dose

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 some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. Patients with signs and symptoms of hepatitis must seek medical evaluation immediately and should be advised to discontinue Apo-TriAvir.

Skin Reactions

Severe, life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, occurring almost exclusively during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome characterized by rash, constitutional findings, and organ dysfunction (see ADVERSE REACTIONS section). Patients should be carefully monitored during the first 18 weeks of treatment. 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 or hypersensitivity reaction. Some of the risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg daily during the 14-day lead-in period and delay in stopping the nevirapine treatment after the onset of the initial symptoms.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day, which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved. Patients should be monitored closely if an isolated rash of any severity occurs.

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.

Women appear to be at higher risk than men of developing rash with nevirapine.

In a clinical trial, the concomitant use of prednisone was associated with an increase in the incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, the use of prednisone to prevent nevirapine-associated rash is not recommended.

Management of Rash Events with Nevirapine*

Patient Management

The recommended 14-day, 200 mg once-daily lead-in dose, prior to escalation to 200 mg twice daily, has been shown to reduce the frequency of rash and must be strictly followed

Do not increase the dose of nevirapine in the presence of rash

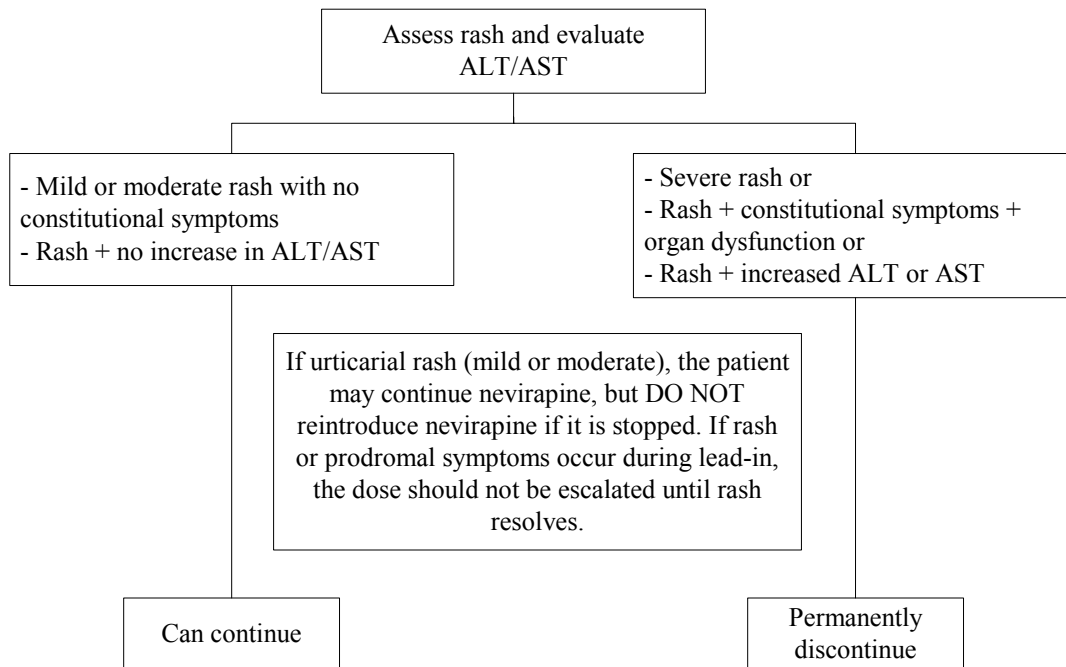
If nevirapine is interrupted for >7 days, reintroduce with the 14-day, 200 mg once-daily lead-in dose

It is suggested that nevirapine and other medications that often cause rash should not be started simultaneously

Prednisone should not be used to prevent rash. Prednisone administration during the first 2 weeks of therapy with nevirapine appears to increase the incidence of rash

Antihistamines do not appear to be effective in preventing rash with nevirapine

Rash Management Algorithm



Definitions

- Mild to moderate rash may include:
 - Erythema
 - Diffuse erythamous or maculopapular rash
- Severe rash may include:
 - Extensive erythamous or maculopapular rash
 - Rash with moist desquamation
 - Rash with angioedema
 - Serum sickness-like reaction
 - Stevens-Johnson syndrome (SJS)
 - Toxic epidermal necrolysis (TEN)
 - Urticardia: pruritic raised rash with welts (may be mild, moderate or severe)
 - Constitutional symptoms include fever, blistering, oral erosive lesions, conjunctivitis, facial edema, and myalgia/arthritis

***Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included severe cases of SJS, TEN, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing sign and symptoms of severe skin reactions or hypersensitivity reactions must discontinue Apo-TriAvir as soon as possible.**

Lactic Acidosis/Severe Hepatomegaly with Steatosis

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

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Caution should be exercised when administering Apo-TriAvir to any patient, and particularly to those with known risk factors for liver disease. Treatment with Apo-TriAvir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Post-Treatment Exacerbations of Hepatitis B

In clinical trials with 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 be self-limited, they may have more severe consequences in patients with decompensated liver disease and 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.

Pancreatitis in Pediatric Patients

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, Apo-TriAvir should be used with caution. Treatment with Apo-TriAvir should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS section).

Serious Adverse Reactions

Zidovudine

Several serious adverse events have been reported with use of zidovudine in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been

associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of zidovudine.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see **DRUG INTERACTIONS** section).

Lamivudine

Several serious adverse events have been reported with use of lamivudine in clinical practice. Reports of anaphylaxis, rhabdomyolysis and peripheral neuropathy have been rare (< 1 in 1000) (see **DRUG INTERACTIONS** section).

Patients receiving Apo-TriAvir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close observation by physicians experienced in the treatment of patients with HIV-associated diseases.

It is recommended that the dose of lamivudine be reduced for adults with body weight below 50 kg (110 lb.), therefore a patient may be on a reduced dose of lamivudine and a standard dose of zidovudine and would not be a candidate for the use of Apo-TriAvir tablets. See complete prescribing information for lamivudine and zidovudine for dosage adjustment.

Post-exposure Prophylaxis:

Nevirapine is not recommended for post-exposure prophylaxis. In the setting of post-exposure prophylaxis, an unapproved use, serious hepatotoxicity, including one instance of liver failure requiring transplantation, and serious skin rash including Stevens-Johnson syndrome, have been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in combination with other antiretroviral agents.

Endocrine and Metabolism

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Hematologic

Very rare occurrences of pure red cell aplasia have been reported with lamivudine or zidovudine use. Discontinuation of lamivudine and/or zidovudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine or zidovudine-induced pure red cell aplasia.

Bone Marrow Suppression

Apo-TriAvir should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm³ or hemoglobin <9.5 g/dL. In patients with advanced symptomatic disease, anemia and granulocytopenia were the most

significant adverse events observed (see **ADVERSE REACTIONS** section). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Immune

Immune Reconstitution: During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment.

Myopathy

Myopathy and myositis with pathological changes similar to that produced by HIV disease have been associated with prolonged use of zidovudine and may occur with Apo-TriAvir therapy.

Renal

Patients with impaired renal function may be at a greater risk of toxicity from Apo-TriAvir due to decreased renal clearance of the drug. Therefore a dosage adjustment of lamivudine and zidovudine may be necessary. It is recommended that Apo-TriAvir not be used in patients with reduced renal function (creatinine clearance ≤ 50 mL/min). For these patients, it is recommended that lamivudine and zidovudine be administered. The individual Product Monographs for lamivudine and zidovudine should be consulted for appropriate dosage adjustments.

In renal dysfunction, a single dose study suggested that patients with a creatinine clearance ~ 20 mL/min do not require an adjustment in nevirapine dosing (see **DETAILED PHARMACOLOGY** section).

Special Populations

Pregnant Women

Apo-TriAvir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There have been no adequate and well controlled studies of nevirapine or Apo-TriAvir in pregnant women, nor are there reports of infants born to women who conceived while receiving Apo-TriAvir.

Consistent with passive transmission of the drug across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum.

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal fetal HIV-transmission. Congenital abnormalities occurred with similar frequency between infants born to mothers who received zidovudine and infants born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

The long-term consequences of in utero and infant exposure to zidovudine are unknown. The long-term effects of early or short-term use of zidovudine in pregnant women are also unknown.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Reproductive studies with lamivudine in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine induced early embryoletality when lamivudine was administered to pregnant rabbits at exposure levels comparable to those achieved in man.

Because animal reproduction studies are not always predictive of the human response, Apo-TriAvir should be used during pregnancy only if the potential benefit outweighs any possible risk.

Nursing Women

Since zidovudine, lamivudine, nevirapine and HIV virus pass into breast milk it is recommended that mothers taking Apo-TriAvir do not breast feed their infants to avoid risking postnatal transmission of infection and potential adverse effects of the drugs in nursing infants.

Zidovudine is excreted in human milk. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum. Mothers should be instructed to discontinue nursing if they are receiving Apo-TriAvir.

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum.

Preliminary results from a pharmacokinetic study (ACTG 25) of 10 HIV-1 infected pregnant women who were administered a single oral dose of 100 or 200 mg nevirapine at a median of 5.8 hours before delivery, indicated that nevirapine readily crosses the placenta and is found in breast milk (breast milk samples taken from 3 out of 10 mothers).

Pediatrics

There are no data on the use of Apo-TriAvir in pediatric patients (see **DETAILED PHARMACOLOGY: Pharmacokinetics** section).

Apo-TriAvir is not recommended in children less than 15 years of age (see **DOSAGE AND ADMINISTRATION** section).

Geriatrics (>55 years of age)

Nevirapine pharmacokinetics in HIV-1 infected adult males and females do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

Ethnic Origin

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median $C_{\text{minss}} = 4.7 \mu\text{g/mL}$ Black, $3.8 \mu\text{g/mL}$ Hispanic, $4.3 \mu\text{g/mL}$ Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Gender

In general, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of Apo-TriAvir therapy are at higher risk for symptomatic hepatic events due to nevirapine. In a retrospective review of nevirapine symptomatic hepatic adverse events, women with CD4 counts $> 250 \text{ cells/mm}^3$ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts $< 250 \text{ cells/mm}^3$ (11.0% versus 0.9%). An increased risk was also observed in men with CD4 counts $> 400 \text{ cells/mm}^3$ (6.3% versus 2.3% for men with CD4 counts $< 400 \text{ cells/mm}^3$) (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reactions Overview

The most serious adverse reactions associated with Apo-TriAvir (nevirapine component) are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Clinical hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and renal dysfunction. Severe and life-threatening hepatic injury, and fatal fulminant hepatitis, have been reported in patients treated with nevirapine. The first 18 weeks of treatment is a critical period, but such events may also occur later. The risk of hepatic events is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. (see **WARNINGS AND PRECAUTIONS).**

Hepato-Biliary

In controlled clinical trials, clinical hepatic events regardless of severity occurred in 4.0% (range 2.5% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Transaminase elevations (ALT or AST $> 5\text{X ULN}$) were observed in 8.8% of patients receiving nevirapine and 6.2% of patients in control groups in clinical trials. In a retrospective analysis of controlled and uncontrolled clinical trials, patients with higher CD4 counts at initiation of

nevirapine therapy, particularly women, were at greater risk for acute symptomatic hepatic events, including death, especially in the first six weeks of therapy.

Patients with chronic hepatitis B or C infection were at higher risk for later hepatic events (see **WARNINGS AND PRECAUTIONS**).

Skin and Subcutaneous Tissues

The most common clinical toxicity of nevirapine is rash. In placebo-controlled trials involving 1374 patients treated with nevirapine (Table 1), rash, of all grades and causality occurred in 14-20% of patients treated with nevirapine. Severe or life-threatening rash occurred in approximately 2% of nevirapine-treated patients, almost exclusively within the first 6 weeks of therapy.

Rashes were usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angio-oedema and urticaria) have been reported. Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. Based on a denominator of 2861 nevirapine-treated clinical trial patients, the overall incidence of SJS was 0.3% (9/2861).

Rashes occur alone or in the context of a hypersensitivity syndrome characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Table 1: RISK OF RASH (%) IN ADULT PLACEBO CONTROLLED TRIALS¹ – REGARDLESS OF CAUSALITY

	Nevirapine	Placebo
	n=1374 %	n=1331 %
Through 6 weeks of treatment²		
Rash events of all grades ³	14.8	5.9
Grade 1 Erythema, pruritus	8.5	4.2
Grade 2 Diffuse maculopapular rash, dry desquamation	4.8	1.6
Grade 3 or 4 Grade 3: vesiculation, moist desquamation, ulceration; Grade 4: erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	1.5	0.1
Through 52 weeks of treatment²		
Rash events of all grades ³	24.0	14.9
Grade 1 See above	15.5	10.8
Grade 2 See above	7.1	3.9
3 or Grade 4 See above	1.7	0.2
Proportion of Patients who Discontinued Treatment Due to Rash	4.3	1.2

- 1 Trials 1037, 1038, 1046 and 1090
- 2 % based on Kaplan-Meier probability estimates
- 3 NCI grading system

Clinical Trial Adverse Drug Reactions (nevirapine)

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

Table 2: Percentage of patients with moderate or severe drug related events in adult placebo-controlled trials

	Trial 1090¹		Trials 1037, 1038, 1046²	
	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
Abnormal LFTs	1.2	0.9	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

¹ Background therapy included lamivudine for all patients and combinations of NRTIs and Pls. Patients had CD4+ counts <200 cells/mm³.

² Background therapy included ZDV and ZDV+ddl; nevirapine monotherapy was administered in some patients. Patients had CD4+ >200 cells/mm³.

Laboratory Abnormalities:

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFT5), including ALT, AST, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis, have been reported in patients treated with nevirapine.

Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 3). 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 (Table 3).

Table 3: Percentage of patients with marked laboratory abnormalities

	Trial 1090¹		Trials 1037, 1038, 1046²	
	Nevirapine n = 1121	Placebo n = 1128	Nevirapine n = 253	Placebo n = 203
Laboratory Abnormality				
Hematology				
Hemoglobin 80 g/L	3.2%	4.1%	0%	0%
Platelets <50 x 10 ⁹ /L	1.3	1	0.4	1.5
Neutrophils < 750 x 10 ⁶ /L	13.3	13.5	3.6	1
Blood Chemistry				
AST >250 U/L	3.7	2.5	7.6	1.5

ALT >250 U/L	5.3	4.4	14	4
Bilirubin >42.5 µm/L	1.7	2.2	1.7	1.5

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

² Background therapy included ZDV and ZDV+ddl; nevirapine monotherapy was administered in some patients. Patients had CD4+ ≥200 cells/mm³.

Because clinical hepatitis has been reported in niverapine-treated patients, intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment. Monitoring should continue at frequent intervals thereafter, depending on the patient's clinical status (see **WARNINGS AND PRECAUTIONS** section).

Post-marketing Experience:

In addition to the adverse events identified during 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 section), redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS: Fat Redistribution section)
Gastrointestinal:	vomiting
Liver and Biliary:	jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
Hematology:	anemia (more commonly observed in children), eosinophilia, neutropenia
Musculoskeletal:	arthralgia
Neurologic:	paraesthesia
Skin and Appendages:	allergic reactions including anaphylaxis, angioedema, bullous eruptions. ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise or significant hepatic abnormalities (see WARNINGS AND PRECAUTIONS section) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia and/or renal dysfunction have been reported with the use of nevirapine.

Apart from rash and abnormal LFTs, the most frequently reported adverse events related to nevirapine therapy across all clinical trials were nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain and myalgia. In very rare instances, cases of anaemia and neutropeflia may be associated with nevirapine therapy. Arthralgia has been reported as a stand-alone event

in rare instances in patients receiving nevirapine containing regimens.

The following events have also been reported when nevirapine has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other anti-retroviral agents and may be expected to occur when nevirapine is used in combination with other agents.

In summary the list of side effects, which can be expected with nevirapine treatment, includes:

- rash (including severe and life-threatening skin reactions including fatal cases of SJS/TEN)
- Hypersensitivity syndrome characterised by rash associated with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, renal dysfunction or other visceral involvement has also been reported.
- abnormal LFTs, (AST, ALT, GGT, total bilirubin, alkaline phosphatase)
- jaundice
- hepatitis, including severe and life-threatening hepatotoxicity and fatal fulminant hepatitis
- nausea
- fatigue
- fever
- headache
- vomiting
- diarrhea
- abdominal pain
- myalgia
- arthralgia
- granulocytopenia
- allergic reaction (anaphylaxis, angio-edema, urticaria)
- anemia

Clinical Trial Adverse Drug Reactions (zidovudine/ lamivudine)

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a human bioequivalence trial, the clinical adverse events associated with lamivudine/zidovudine combination in 24 subjects were similar when compared to lamivudine 150 mg plus zidovudine 300 mg administered as separate tablets. All reported adverse events were mild in intensity. The most frequently reported adverse events after single-dose administration were headache or dizziness (seven events in six subjects) and nausea (four events

in four subjects). Other reported adverse events included pruritus, skin lesion, visual disturbance, rhinorrhea, and phlebitis (one event in one subject, each). Ten events in seven subjects were assessed by the investigator as possibly or probably drug related and included headache, nausea, phlebitis, and disturbance of vision.

The safety of chronic dosing with lamivudine/zidovudine combination has not been assessed but is not expected to be different from the safety profiles of lamivudine and zidovudine administered concurrently as separate formulations. In four randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected clinical adverse events were observed (see Table 4).

Table 4: Selected clinical adverse events (≥5% frequency) in four controlled clinical trials with lamivudine 300 mg/day and zidovudine 600 mg/day

Adverse Event	lamivudine plus zidovudine (n=251)
Body as a whole	
Headache	35%
Malaise & fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea & vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous System	
Neuropathy	12%
Insomnia & other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs & symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Other clinical adverse events reported in controlled clinical trials in association with lamivudine 150 mg b.i.d. plus zidovudine 600 mg per day in at least 1% of patients were:

Gastrointestinal: Abdominal discomfort and pain (3%), abdominal distension (3%), dyspepsia (2%), gastrointestinal discomfort and pain (3%), gastrointestinal gas (4%), hyposalivation (2%), oral ulceration (1%).

- Musculoskeletal:** Muscle atrophy/weakness/tiredness (1%), muscle pain (2%).
- Neurological:** Mood disorders (1%), sleep disorders (4%), taste disturbances (1%).
- Other:** Breathing disorders (2%), general signs and symptoms (1%), pain (2%), sexual function disturbances (1%), temperature regulation disturbance (1%).
- Skin:** Pruritis (1%), skin rashes (1%), sweating (1%).

Pancreatitis was observed in three of the 656 adult patients (<0.5%) who received lamivudine in controlled clinical trials.

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

Table 5: Frequencies of selected laboratory abnormalities among adults in four controlled clinical trials of lamivudine 300 mg/day plus zidovudine 600 mg/day*

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

ULN = Upper limit of normal

ANC = Absolute neutrophil count

n = Number of patients assessed

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

Post-Market Adverse Drug Reactions

The following events have been identified during post-approval use of lamivudine and/or zidovudine alone or in combination with other antiretroviral therapy in clinical practice. 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 either their seriousness, frequency of reporting, causal connection to lamivudine and/or zidovudine, or a combination of these factors.

- Body as a Whole:** Redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS: Fat Redistribution** section).
- Cardiovascular:** Cardiac arrest, cardiac failure, cardiomegaly, cardiomyopathy, cerebrovascular accident, hypertension, hypotension, intracranial hemorrhage,

orthostatic hypotension, palpitation(s), syncope, tachycardia, vasculitis, vasodilation.

Endocrine and Metabolic:

Acidosis, anorexia, dehydration, gynecomastia, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypoglycemia, hyponatremia, inappropriate antidiuretic hormone secretion, increased appetite, increased CPK, increased LDH, increased serum iron, lactic acidosis and hepatic steatosis (see **WARNINGS AND PRECAUTIONS** section), weight loss.

Eye:

Conjunctivitis, retinitis, visual field defect.

Gastrointestinal:

Abdominal distention, ascites, bleeding gums, constipation, diarrhea, discoloration of tongue, dyspepsia, dysphagia, edema of the tongue, esophagitis, esophageal ulcer, flatulence, gastritis, gastrointestinal hemorrhage, mouth ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, sialoadenitis, stomatitis.

General:

Abdominal pain, allergic reaction, anaphylaxis, back pain, Candida infection, chills, chest pain, death, edema of face, edema of extremities, fatigue, fever, flu syndrome, hypertonia, hypotonia, malaise, pain, pallor, sepsis, weakness.

Hemic and Lymphatic:

Abnormalities of red cells, abnormality of white cells, agranulocytosis, anemia, aplastic anemia, bone marrow depression, eosinophilia, hemolysis, impaired red cell maturation, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, lymphoma, methemoglobinemia, neutropenia, pancytopenia, pure red cell aplasia, sarcoma, splenomegaly, thrombocytopenia, thrombotic thrombocytopenic purpura.

Hepatobiliary Tract and Pancreas:

Cholestatic jaundice, fatty liver, hepatic impairment, hepatic failure, hepatitis, hepatomegaly, hyperbilirubinemia, increased aminotransferase levels, increased amylase, jaundice, pancreatitis.

Musculoskeletal:	Amyotrophy, arthralgia, muscle disorders including rarely rhabdomyolosis, myositis, tremor, twitch, myalgia, hemarthrosis, leg cramps.
Nervous:	Aggressive behavior, agitation, amnesia, anxiety, ataxia, confusion, convulsions, delusions, dementia, depression, dizziness, dystonic movement(s), emotional lability, encephalitis, facial palsy, hallucinations, headache, hypoesthesia, insomnia, loss of mental acuity, meningitis, myasthenia, nervousness, mania, paresthesia, paranoia, peripheral neuritis, peripheral neuropathy, personality disorder, psychotic disorders, somnolence, tremor, vertigo.
Reproductive:	Amenorrhea, decreased libido, impotence, intermenstrual bleeding.
Respiratory:	Apnea, cough, dyspnea, epistaxis, hyperventilation, influenza, pharyngitis, pneumonia, rhinitis, sinusitis.
Skin:	Acne, alopecia, changes in skin and nail pigmentation, dryness of skin, erythema multiforme, exfoliative dermatitis, hair color change, hirsutism, hyperpigmentation, maculopapular lesions, nail disorders, photosensitivity, pruritus, rash, rubelliform rash, Stevens-Johnson syndrome, sweating, urticaria, vesiculobullous rash.
Special Senses:	Ageusia, amblyopia, hearing loss, photophobia, taste disturbance, speech disorder, tinnitus.
Urogenital:	Albuminuria, dysuria, hematuria, increased creatinine levels, polyuria, renal dysfunction, renal failure, urinary frequency.

DRUG INTERACTIONS

Serious Drug Interactions

- See Table 7 for the changes in pharmacokinetic parameters of co-administered drugs
- See Table 8 for drugs that require an alteration in dose or regimen
- See Table 9 for drugs that may need a dose adjustment

OVERVIEW of NEVIRAPINE

Cytochrome P450

Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A4 and 2B6. Co-administration of nevirapine and drugs primarily metabolized by CYP3A4 or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

Table 6 contains the results of drug interaction studies performed with nevirapine and other drugs likely to be co-administered. The effects of nevirapine on the AUC, C_{max}, and C_{min} of co-administered drugs are summarized. To measure the full potential pharmacokinetic interaction effect following induction, patients on the concomitant drug at steady state were administered 28 days of nevirapine (200 mg QD for 14 days followed by 200 mg BID for 14 days) followed by a steady state reassessment of the concomitant drug. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 7. The data in Tables 6 and 7 are 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 7. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 8, additional clinical monitoring may be warranted when co-administering these drugs.

Table 6: Drug Interactions: Changes in pharmacokinetic parameters for co-administered drug in the presence of nevirapine (all interaction studies were conducted in HIV-1 positive patients)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	C _{max}	C _{min}
Antiretrovirals				AUC	C _{max}	C _{min}
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§
Efavirenz ^a	600 mg QD	200 mg QD x 14 days; 400 mg BID x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓34 to ↑1)	↓32 (↓35 to ↓19)
Indinavir ^a	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir ^{a,b}	300/75 mg/m ² (lopinavir/ritonavir) ^b	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 ^c	↓14 (↓36 to ↑16)	↓22 (↓44 to ↑9)	↓55 (↓75 to ↓9)
Lopinavir ^a	400/100 mg (lopinavir/ritonavir)	200 mg QD x 14 days; 200 mg BID > 1 year	22, 19 ^c	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Nelfinavir ^a	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	↔	↔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)

Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	↔
Sequinavir ^a	600 mg TID	200 mg QD x 14 days; 200 mg BID x 21 days	23	↓38 (↓47 to↓11)	↓32 (↓44 to↓6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	↔	↔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to↓4)	↓30 (↓51 to↑14)	§
Other Medications				AUC	C _{max}	C _{min}
Clarithromycin ^a	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to↓24)	↓23 (↓31 to↓14)	↓57 (↓70 to↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to↑73)	↑47 (↑21 to↑80)	↔
Ethinyl estradiol ^a and Norethindrone ^a	0.35 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to↓3)	↔	§
				↓19 (↓30 to↓7)	↓16 (↓27 to↓3)	§
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole ^a	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to↓60)	↓44 (↓58 to↓27)	§
Rifabutin ^a	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to↑40)	↑28 (↑9 to↑51)	↔
Metabolite 25 O-desacetyl-rifabutin				↑24 (↓16 to↑84)	↑29 (↓2 to↑68)	↑22 (↓14 to↑74)
Rifampin ^a	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to↑28)	↔	§

§ = C_{min} below detectable level of the assay

↑ = Increase, ↓ = Decrease, ↔ = No Effect

^a For information regarding clinical recommendations see Table 8

^b Pediatric subjects ranging in age from 6 months to 12 years

^c Parallel group design; n for nevirapine + lopinavir/ritonavir, n for lopinavir/ritonavir alone

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV therapy) the effect of the concomitant drug on plasma nevirapine steady state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data (Table 7). The effect of other drugs listed in Table 6 on nevirapine pharmacokinetics was not significant.

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

Table 7: Established Drug Interactions: Alteration in dose or regimen may be recommended based on drug interaction studies (see Table 8 for magnitude of interaction)

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 lowered. Alternatives to clarithromycin, 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.
Indavir	↓ Indavir	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	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Methadone	↓ Methadone ^a	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	↓ Nelfinavir M8 metabolite ↓ Nelfinavir C _{min}	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.
Sequinavir	↓ Sequinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

^a Based on reports of narcotic withdrawal syndrome in patients treated with nevirapine and methadone concurrently, and evidence of decreased plasma concentrations of methadone.

Nucleoside Reverse Transcriptase Inhibitors

No dosage adjustments are required when nevirapine is taken in combination with ZDV, ddl or ddC. In a subset of patients (n=6) who were administered nevirapine 400 mg/day and ddl on a background of ZDV therapy, nevirapine produced a significant decline of 32% in ZDV AUC and a non-significant decline of 27% in ZDV C_{max}. When the ZDV data were pooled from two studies (n=33) in which HIV-1 infected patients received nevirapine 400 mg/day either alone or in combination with 200-300 mg/day ddl or 0.375 to 0.75 mg/day ddC on a background of ZDV therapy, nevirapine produced a non-significant decline of 13% in ZDV AUC and a non-significant increase of 5.8% in ZDV C_{max}. Paired data suggest that ZDV had no effect on the steady-state pharmacokinetics of nevirapine. In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of either ddl (n=18) or ddC (n=6).

Results from a 36 day study in HIV infected patients (n=25) administered nevirapine, nelfinavir (750 mg t.i.d.) and stavudine (3040 mg, b.i.d.) showed no statistically significant changes in the AUC or C_{max} of stavudine. Furthermore, a population pharmacokinetic study of 90 patients assigned to receive lamivudine with nevirapine or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.

Lamivudine

A population pharmacokinetic study of 90 patients assigned to receive lamivudine with nevirapine or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.

Table 8: 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	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Use of Nevirapine During Pregnancy

Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There have been no adequate and well-controlled studies of nevirapine in pregnant women, nor are there reports of infants born to women who conceived while receiving nevirapine chronic dosing in clinical trials.

Labour, Delivery and Nursing Mothers

It is currently recommended that HIV-1 infected women should not breast feed infants regardless of the use of antiretroviral agents, to avoid post-natal transmission of HIV-1. The effect of nevirapine in small infants is unknown at this time.

Preliminary results from a pharmacokinetic study (ACTG 25) of 10 HIV-1-infected pregnant women who were administered a single oral dose of 100 or 200 mg nevirapine at a median of 5.8 hours before delivery, indicated that nevirapine readily crosses the placenta and is found in breast milk (breast milk samples taken from 3 out of 10 mothers).

Gender

In general, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/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 also observed in men with CD4 counts > 400 cells/mm³ (6.3% versus 2.3% for men with CD4 counts <400 cells/mm³) (see **ADVERSE REACTIONS** section).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Occupational Hazards: Psychomotor Performance

There are no specific studies assessing psychomotor performance in patients using nevirapine. Somnolence has been reported in association with nevirapine therapy; if this occurs during nevirapine administration patients should be advised to refrain from driving a motor vehicle or operating potentially hazardous machinery.

Pediatric Use

Safety and effectiveness of nevirapine in HIV-1-infected pediatric patients younger than 15 years of age have not been established.

Protease Inhibitors

There were no increased safety concerns noted with concomitant administration of nevirapine with any of the protease inhibitors. In the following four studies, nevirapine was given 200 mg once daily for two weeks followed by 200 mg twice daily for 28 days:

Ritonavir

No dosage adjustments are required when nevirapine is taken in combination with ritonavir. Results from a clinical trial (n=25) with HIV infected patients administered nevirapine and

ritonavir (600 mg b.i.d. [using a gradual dose escalation regimen]) indicated that their co-administration leads to no significant change in ritonavir or nevirapine plasma concentrations.

Indinavir

Results from a clinical trial (n=25) with HIV infected patients administered nevirapine and indinavir (800 mg q8h) indicated that their co-administration leads to a 28% mean decrease ($p < 0.01$) in indinavir AUC and a 38% mean decrease in indinavir C_{\min} ($p < 0.01$). There was no significant change in nevirapine plasma levels. No definitive clinical conclusions have been reached regarding the potential impact of co-administration of nevirapine and indinavir. A dose increase of indinavir to 1000 mg q8h may be considered when indinavir is given with nevirapine 200 mg b.i.d.; however, there are no data currently available to establish that the short term or long term safety or antiviral activity of indinavir 1000 mg q8h with nevirapine 200 mg b.i.d. will differ from that of indinavir 800 mg q8h with nevirapine 200 mg b.i.d.

Saquinavir

Results from a clinical trial (n=31) with HIV infected patients administered nevirapine and saquinavir (hard gelatine capsules; 600 mg t.i.d.) indicated that their co-administration leads to a mean reduction of 24% ($p=0.041$) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir levels due to this interaction may further reduce the plasma levels of saquinavir, which are achieved with the hard gelatine capsule formulation. The clinical significance of this interaction is not known. Co-administration did not affect the pharmacokinetics of nevirapine.

Nelfinavir

Results from a 36 day study in HIV infected patients (n=25) administered nevirapine, nelfinavir (750 mg t.i.d.) and stavudine (d4T) (30-40 mg b.i.d.) showed no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC +4%, C_{\max} +14% and C_{\min} -2%). Compared to historical controls nevirapine levels appeared to be unchanged.

The major metabolite of nelfinavir (M8), which has comparable activity to the parent compound, however, has a 62% mean decrease in AUC with a 59% decrease in C_{\max} and 66% decrease in C_{\min} . The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.

Lopinavir/ritonavir

Nevirapine, used in combination with lopinavir/ritonavir 400/100 mg (3 capsules) twice daily resulted in a decline in the mean lopinavir AUC of 27% and a decrease in the C_{\max} and C_{\min} , of 19% and 51% respectively. An increase in the dose of lopinavir/ritonavir to 533/133 mg twice daily (4 capsules) with food is recommended in combination with nevirapine. Results from a pharmacokinetic study in pediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. A dose increase 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 in children 6 months to 12 years of age may be considered when used in combination with nevirapine in patients where reduced susceptibility to lopinavir/ritonavir is clinically suspected (by treatment history or laboratory evidence).

Oral Contraceptives

Nevirapine 200 mg b.i.d. was co-administered with a single dose of an oral contraceptive containing ethinyl estradiol (17- α EE) 0.035mg and norethindrone (NET) 1.0 mg (OrthoNovum® 1/35). Compared to plasma concentrations observed prior to nevirapine administration, the median AUC for 17 α -EE was significantly decreased by 29% after 28 days of nevirapine dosing. There was a significant reduction in EE mean resident time and half-life. There was a significant reduction (18%) in median AUG for NET, without changes in mean resident time or half-life. The magnitude of the effect suggests that the dose of the oral contraceptive could be adjusted to allow adequate treatment for indications other than contraception (e.g., endometriosis), if used with nevirapine. However, the risk of oral contraceptive failure is a possibility if estrogen/progesterone-containing oral contraceptives are used. Other means of contraception (such as barrier methods) are recommended, when nevirapine is administered to women of child-bearing potential. For other therapeutic uses requiring hormonal regulation, the therapeutic effect in patients being treated with nevirapine should be monitored.

Methadone

There have been reports of narcotic withdrawal symptoms in patients receiving methadone treatment concomitantly with nevirapine. Nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

CYP Isozyme Inducers

Rifampin

In an open label study (n=14), rifampin produced a significant lowering of nevirapine AUC (58%), C_{max} (-50%) and C_{min} (-68%) compared to historical data. In contrast, the effects of nevirapine on the steady state pharmacokinetics of rifampin resulted in no significant change in rifampin C_{max} and AUG. Rifampin and nevirapine should, therefore, not be used concomitantly and physicians wanting to use rifampin for treatment of mycobacterial infections in those patients taking nevirapine should consider rifabutin instead (see **WARNINGS AND PRECAUTIONS** section).

Rifabutin

In an open label study (n=19), administration of nevirapine 200 mg b.i.d. with rifabutin 300 mg daily (or 150 mg daily if concomitantly receiving ZDV or protease inhibitors), resulted in non-significant changes to rifabutin concentrations (12% median increase in rifabutin AUG and a 3% median decrease in rifabutin C_{minss}), and a significant increase (20%) in median C_{maxss} . There were no significant changes in the active metabolite 25-O-desacetyl-rifabutin concentrations. In the same study, rifabutin administration resulted in an apparent significant increase in systemic clearance of nevirapine by 9% compared to historical controls. None of these changes are considered to be clinically important. Nevirapine and rifabutin can safely be administered concurrently with no dose adjustments required.

CYP Isozyme Inducers

Ketoconazole

Administration of nevirapine 200 mg b.i.d. with ketoconazole 400 mg q.d. resulted in a significant reduction (63% median reduction in ketoconazole AUG and a 40% median reduction in ketoconazole C_{max}). In the same study, ketoconazole administration resulted in a 15-28% increase in the plasma levels of nevirapine compared to historical controls. Ketoconazole and nevirapine should not be given concomitantly. The effects of nevirapine on itraconazole are not known. Although interaction studies have not been performed, antifungal medicinal products, which are eliminated renally (e.g. fluconazole) might be substituted for ketoconazole. (See **WARNINGS AND PRECAUTIONS** section).

Fluconazole

Co-administration of fluconazole and nevirapine resulted in approximately 100% increase in nevirapine exposure compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine on fluconazole.

Clarithromycin

Results of a nevirapine -clarithromycin drug-drug interaction study (n=15) resulted in a significant reduction in clarithromycin AUG (-31%), C_{max} (-23%) and C_{min} (-57%), but a significant increase in AUG (42%) and C_{max} (47%) of the active metabolite 14-OH clarithromycin. There was a significant increase in the nevirapine C_{min} (28%) and a non-significant increase in nevirapine AUG (26%) and C_{max} (24%). These results would suggest that no dose adjustment is necessary in either drug when the two drugs are co-administered. However, alternative therapy to clarithromycin should be considered when treating a patient for Mycobacterium avium-intracellulare complex, as the active metabolite is not effective in this instance.

Other Drug Metabolized by CYP3A

Biotransformation of nevirapine involves extensive cytochrome P450 metabolism (CYP3A>CYP2B6) and glucuronidation with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Available data on the potential interaction between nevirapine and other drugs that are extensively metabolized by CYP3A are limited and preliminary; therefore, careful monitoring of the therapeutic effectiveness of CYP3A-metabolized drugs is recommended when taken in combination with nevirapine.

Drug-Herb Interactions

St. John's Wort

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

Drug Lifestyle Interactions

Occupational Hazards: Psychomotor Performance:

There are no specific studies assessing psychomotor performance in patients using Apo-TriAvir.

Somnolence has been reported in association with nevirapine therapy; if this occurs during Apo-TriAvir administration, patients should be advised to refrain from driving a motor vehicle or operating potentially hazardous machinery.

In Vitro Studies

Studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapsone, rifabutin, rifampin and trimethoprim/sulphamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites.

DRUG INTERACTIONS

OVERVIEW OF ZIDOVUDINE/LAMIVUDINE

Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine had no effect on the pharmacokinetics of lamivudine (see **ACTION AND CLINICAL PHARMACOLOGY** section).

The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route of elimination is renal.

Table 9: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Atovaquone	Decrease in zidovudine clearance.	Data from 14 HIV-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a 24% ± 12% decrease of zidovudine oral clearance, leading to a 35% ± 23% increase in plasma zidovudine AUC. The glucuronide Metabolite: parent ratio decreased from a mean of 4.5 when zidovudine was administered alone to 3.1 when zidovudine was administered with atovaquone tablets. Zidovudine had no effect on atovaquone pharmacokinetics.
Bone marrow suppressive agents/cytotoxic agents	Coadministration may increase risk of hematologic toxicity.	Coadministration of zidovudine with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g. dapsone, flucytosine, vincristine, vinblastine, or adriamycin) may increase the risk of hematologic toxicity.
Fluconazole	Fluconazole interferes with the oral clearance and metabolism of zidovudine.	Preliminary data suggests that fluconazole interferes with the oral clearance and metabolism of zidovudine. In a pharmacokinetic interaction study in which 12 HIV-positive men received zidovudine alone and in combination with fluconazole, increases in the mean peak serum concentration (79%), AUC (70%) and half-life (38%) were observed at steady state. The clinical significance of this interaction is unknown.
Ganciclovir	Coadministration increases the risk of hematologic toxicities in some patient with advanced HIV disease.	Use of zidovudine in combination with ganciclovir increases the risk of hematologic toxicities in some patients with advanced HIV disease. Should the use of this combination become necessary in the treatment of patients with HIV disease, dose reduction or interruption of one or both agents may be necessary to

		minimize hematologic toxicity. Hematologic parameters, including hemoglobin, hematocrit, and white blood cell count with differential, should be monitored frequently in all patients receiving this combination.
Interferon-alpha	Hematologic toxicities have been seen when zidovudine is used concomitantly with interferonalpha.	As with the concomitant use of zidovudine and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.
Methadone	Plasma levels of zidovudine can be elevated in some patients while remaining unchanged in others.	In a pharmacokinetic study of 9 HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of zidovudine every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with zidovudine and after 14 days of treatment with zidovudine. No adjustments in methadone-maintenance requirements were reported. However, plasma levels of zidovudine were elevated in some patients while remaining unchanged in others. The exact mechanism and clinical significance of these data are unknown.
Phenytoin	A decrease in oral zidovudine clearance.	Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300 mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.
Probenecid	May increase zidovudine levels.	Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or reducing renal excretion of zidovudine. Some patients who have used zidovudine concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.
Trimethoprim, a constituent of cotrimoxazole	Administration of trimethoprim, a constituent of co-trimoxazole causes a 40% increase in lamivudine plasma levels.	However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of cotrimoxazole. Administration of cotrimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.
Valproic acid	Increase in zidovudine AUC and a decrease in the plasma GZDV AUC.	The concomitant administration of valproic acid 250 mg (n=5) or 500 mg (n=1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to 6 HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass

		metabolism. Although the clinical significance of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.
Zalcitabine	Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently.	Apo-TriAvir is therefore not recommended to be used in combination with zalcitabine.
Other agents		Preliminary data from a drug interaction study (n=10) suggest that coadministration of 200 mg zidovudine and 600 mg rifampin decreases the area under the plasma concentration curve of zidovudine by an average of 48% ± 34%. However, the effect of once daily dosing of rifampin on multiple daily doses of zidovudine is unknown. In vitro, combinations of zidovudine with either ribavirin or stavudine are antagonistic. The concomitant use of either ribavirin or stavudine with Apo-TriAvir should be avoided.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

A 14-day lead-in period is necessary to begin Apo-TriAvir therapy in order to lessen the frequency of nevirapine-associated rash.

Therefore, during the 14-day lead-in period, the recommended dose for Apo-TriAvir (zidovudine, lamivudine and nevirapine) is one tablet once daily. During the 14-day lead-in, an additional 300 mg zidovudine and 150 mg lamivudine per day should also be prescribed, separated by 12 hours from the Apo-TriAvir dose.

Following the 14-day lead-in period, the recommended dose for Apo-TriAvir (zidovudine, lamivudine and nevirapine) is one tablet twice daily.

It is recommended that the dose of lamivudine be reduced for adults with body weight below 50 kg (110 lb.), therefore a patient may be on a reduced dose of lamivudine and a standard dose of zidovudine and would not be a candidate for the use of Apo-TriAvir tablets.

Dose Adjustment

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 Apo-TriAvir, due to its nevirapine component. The optimal frequency of monitoring during this period has not been established, however it may be prudent to conduct clinical and laboratory monitoring more often than once per month; for example, 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 Apo-TriAvir treatment (see **WARNINGS AND PRECAUTIONS** section).

Apo-TriAvir should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see WARNINGS). Patients experiencing rash during the 14-day lead-in period should not have their Apo-TriAvir dose increased until the rash has resolved (see WARNINGS AND PRECAUTIONS).

Apo-TriAvir administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (> 5X ULN) (excluding GGT), until the liver function test elevations have returned to baseline. APO-TriAvir may then be restarted at the lead-in dose of 1 pill/day. Increasing the daily dose to 1 pill twice daily should be done with caution, after extended observation. Patients should be aware that this may not prevent serious adverse reactions. Apo-TriAvir (and its nevirapine component) should be permanently discontinued if moderate or severe liver function test abnormalities recur (see **WARNINGS AND PRECAUTIONS**).

Patients with Renal Impairment

In End Stage Renal Disease (ESRD) appropriate doses of nevirapine with respect to safety and efficacy have not been established. Subjects with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC over a one week exposure period with an accumulation of nevirapine hydroxy-metabolites in plasma. An additional 200 mg dose of nevirapine following each dialysis treatment is recommended in patients requiring dialysis. In renal dysfunction, a single dose study suggested that patients with a creatinine clearance 20 mL/min do not require an adjustment in nevirapine dosing.

Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require an adjustment in Apo-TriAvir dosing; however, caution should be exercised when Apo-TriAvir is administered to patients with moderate hepatic impairment. Apo-TriAvir should not be administered to patients with severe hepatic dysfunction.

Missed Dose

Patients who miss a dose should take it as soon as they remember and then continue as before. Do not double the next dosage.

Patients who interrupt Apo-TriAvir dosing for more than 7 days should restart using the lead-in dosing described above (see **Recommended Dose and Dose Adjustment**).

OVERDOSAGE

There is no known antidote for Apo-TriAvir (zidovudine, lamivudine and nevirapine). The use of activated charcoal may be helpful.

One case of acute overdose in an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and haematologic tests remained normal. One other adult patient in error ingested lamivudine 1,200 mg per day plus zidovudine 1,200 mg per day for approximately 2 weeks; he had a Grade 3 decrease in absolute neutrophil count that resolved upon reduction of doses of lamivudine and zidovudine. In Phase I studies, lamivudine was administered at doses up to 20 mg/kg per day (i.e., approximately five times the usual

recommended dose in adults) without serious consequences. It is not known whether lamivudine can be removed by peritoneal dialysis or haemodialysis.

Cases of acute overdose of zidovudine in both children and adults have been reported with doses up to 50 grams. None were fatal. The only consistent finding in these cases of overdose was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to zidovudine occurred in a 35-year-old male 3 hours after ingesting 36 grams of zidovudine. No other cause could be identified. All patients recovered without permanent sequelae.

Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV is enhanced.

Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases, and weight decrease. All subsided following discontinuation of nevirapine.

In one case, a patient accidentally ingested nevirapine 1200 mg daily for three days, and then 1800 mg for a fourth day. The patient suffered fever, generalized rash, nausea, vomiting, headache, chills, and facial swelling, and was admitted to hospital for 5 days. The event resolved without sequelae.

In another case, a patient ingested 9 tablets of nevirapine (1800 mg) per day for 10 days. The patient presented with rash (erythema nodosum), pulmonary infiltrate, and bilateral edema of hands and feet. He was hospitalized for 2 weeks during which time he was aggressively diuresed. The events resolved over 3 weeks.

No acute toxicities or sequelae were reported for one patient who ingested 800 mg of nevirapine for one day.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, lamivudine and zidovudine are phosphorylated to their active 5-triphosphate metabolites, lamivudine triphosphate (L-TP) and zidovudine triphosphate (ZDV-TP). *In vitro* L-TP has an intracellular half-life of approximately 10.5 to 15.5 hours. The principal mode of action of L-TP and ZDV-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP is a weak inhibitor of mammalian α , β , and γ -DNA polymerases. ZDV-TP is a weak inhibitor of the cellular DNA polymerase- α and mitochondrial polymerase- γ and has been reported to be incorporated into the DNA of cells in culture.

Nevirapine is a highly selective, non-nucleoside reverse transcriptase inhibitor (NNRTI) of Human Immunodeficiency Virus Type 1 (HIV-1). The enzymatic activity of reverse transcriptase (RT) is required for replication of HIV. Nevirapine binds directly to RT and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The inhibitory activity of nevirapine is not competitive with respect to template or nucleoside triphosphates. Reverse transcriptase from HIV-2 and eukaryotic DNA polymerases (such as human DNA polymerases α , β , γ or δ) are not inhibited by nevirapine.

Pharmacokinetics

The single-dose pharmacokinetic properties of lamivudine and zidovudine have been studied in 24 healthy adult subjects in a single-centre, open label, randomized, three-way crossover study to evaluate the bioequivalence between lamivudine/zidovudine combination and the 150 mg lamivudine tablet and the 300 mg zidovudine tablet given simultaneously.

Lamivudine/zidovudine combination was bioequivalent to one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) when administered to fasting subjects. A summary of the results is provided in Table 10.

Table 10: Summary Table of Measured Comparative Bioavailability Data for Lamivudine and Zidovudine Tablets

	Geometric Mean and Arithmetic Mean (CV)						Ratio of Geometric Means A:B (%) (CI)		Ratio of Geometric Means C:A (%) (CI)	
	Treatment A Combined 150 mg lamivudine and zidovudine 300 mg Fasted		Treatment B lamivudine 150 mg Tablet + zidovudine 300 mg Tablet Fasted		Treatment C Combined 150 mg lamivudine and zidovudine 300 mg Fed					
	ZDV	LAM	ZDV	LAM	ZDV	LAM	ZDV	LAM	ZDV	LAM
AUC _{last} (ng·h/mL)	2266.80 2365.63 (29.6)	5747.93 5896.06 (21.45)	2296.02 2357.09 (23.22)	5931.51 6131.41 (26.37)	2029.33 1810.16 (31.21)	5683.12 5167.96 (18.67)	0.99 (0.91-1.07)	0.97 (0.92-1.03)	0.90 (0.83-0.97)	0.99 (0.93-1.05)
AUC _∞ (ng·h/mL)	2299.44 2398.16 (29.43)	6004.95 6137.56 (20.11)	2329.36 2390.88 (23.13)	6185.54 6374.20 (25.22)	2061.10 2147.63 (30.95)	5932.26 6035.41 (19.23)	0.99 (0.91-1.07)	0.97 (0.92-1.02)	0.90 (0.83-0.97)	0.99 (0.94-1.04)
C _{max} (ng/mL)	1827.27 2008.27 (40.33)	1536.96 1620.28 (32.07)	1883.15 1992.64 (31.92)	1634.32 1742.22 (35.37)	1000.26 1139.24 (51.59)	1311.73 1367.59 (29.53)	0.97 (0.82-1.15)	0.94 (0.84-1.06)	0.55 (0.46-0.65)	0.85 (0.76-0.96)
T _{max} (h)	0.50* 0.57 (80.32)	0.75* 0.91 (53.16)	0.50* 0.58 (58.83)	1.00* 0.91 (40.51)	1.00* 1.07 (61.26)	1.50* 1.86 (50.81)	NA	NA	NA	NA
T _{1/2} (h)	1.48 1.50 (15.73)	9.66 9.98 (27.85)	1.43 1.45 (16.24)	9.52 9.79 (24.71)	1.48 1.53 (26.78)	9.80 10.52 (50.61)	NA	NA	NA	NA

ZDV = zidovudine, LAM = lamivudine

* Median

NA: not applicable

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected

adult patients after administration of single oral, multiple oral and intravenous (IV) doses ranging from 0.25 to 10 mg/kg. After oral administration of 2 mg/kg, the peak plasma lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean \pm S.D.) and half-life was 2.6 ± 0.5 hours. There were no significant differences in half-life across the range of single doses (0.25 to 8 mg/kg). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to dose over the range from 0.25 to 10 mg/kg.

Lamivudine is well absorbed from the gut, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour.

Pharmacokinetic studies of zidovudine following intravenous dosing in adults indicate dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours. Zidovudine is rapidly metabolized in the liver to 3'-azido-3'-deoxy-5'-O- β -D-glucopyranuronosylthymidine (GZDV, formerly called GAZT), and both are rapidly eliminated by the kidney. A second metabolite, 3'-amino-3'-deoxythymidine (AMT) has been identified in the plasma following single dose intravenous administration of zidovudine. After oral dosing in adults, zidovudine is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours, with an average oral bioavailability of 65%.

The pharmacokinetics of nevirapine are characterized by rapid and nearly complete oral absorption, an apparent volume of distribution that exceeds total body water, and a prolonged disposition phase in humans. Nevirapine is approximately 60% bound to plasma proteins in the plasma concentration range of 1-10 μ g/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% of the concentration in plasma; this ratio is approximately equal to the fraction not bound to plasma protein. Nevirapine is extensively biotransformed by cytochrome P450 to several hydroxylated metabolites; *in vitro* studies suggest that this metabolism is mediated primarily by CYP3A, although other CYP isozymes may have a secondary role. The multiple dose pharmacokinetics are characterized by metabolic autoinduction of cytochrome P450 isozymes resulting in a 1.5 to 2 fold increase in nevirapine systemic clearance 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 45 hours (single dose) to approximately 25 to 30 hours with multiple dosing. The pharmacokinetics of nevirapine remain approximately linear in the dose range of 200-400 mg/day following induction.

Special Populations

Renal Impairment

The single dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild ($50 \leq Cl_{cr} < 80$ mL/min), moderate ($30 \leq Cl_{cr} < 50$ mL/min) or severe ($Cl_{cr} < 30$ mL/min) renal impairment or end stage renal disease (ESRD) requiring dialysis and 8 subjects with normal renal function ($Cl_{cr} > 80$ mL/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. Subjects with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC over a one week exposure period with an accumulation of nevirapine hydroxy-metabolites in plasma (see **DOSAGE AND**

ADMINISTRATION section).

For further references about zidovudine and lamivudine see **Part II, Special Populations, Impaired Renal Function**.

Hepatic Impairment

The single-dose pharmacokinetics of nevirapine have been compared in 10 subjects with hepatic impairment and 8 subjects with normal hepatic function. Overall, the results suggest that mild to moderate hepatic impairment (defined as Child-Pugh Classification Score ≤ 7), had no significant effect on the pharmacokinetics of nevirapine. However, the pharmacokinetics of nevirapine in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation (see **DOSAGE AND ADMINISTRATION** section).

Age

Nevirapine pharmacokinetics in HIV-1-infected adult males and females do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

Gender

In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (V_{dss}/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance (24.6 ± 7.7 mL/kg/hr in females vs. 19.9 ± 3.9 mL/kg/hr in males after single dose) or plasma concentrations following either single- or multiple-dose administration(s).

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (37 females, 205 males) revealed no clinically significant difference in nevirapine steady-state trough concentrations (median $C_{minss} = 4.6$ μ g/mL females, 4.2 μ g/mL males) with long-term nevirapine treatment at 400 mg/day.

Ethnic Origin

The pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity. However, an evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median $C_{minss} = 4.7$ μ g/mL Black, 3.8 μ g/mL Hispanic, 4.3 μ g/mL Caucasian) with long-term nevirapine treatment at 400 mg/day.

STORAGE AND STABILITY

Apo-TriAvir (zidovudine, lamivudine and nevirapine) tablets should be stored between 15° and 30°C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Apo-TriAvir (zidovudine, lamivudine and nevirapine) tablets are white to off-white, capsule-shaped tablets, engraved “Apo-TriAvir” on one side and “XCL” on the other side. Available in bottles of 60 tablets.

Composition

Each Apo-TriAvir tablet contains 300 mg of zidovudine, 150 mg of lamivudine, and 200 mg of nevirapine. In addition, each tablet contains the non-medicinal ingredients microcrystalline cellulose, methylcellulose, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

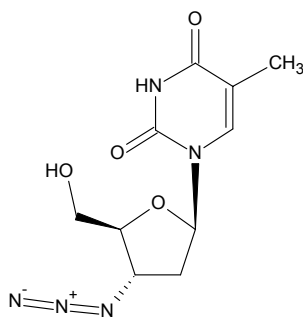
Drug Substance

Proper Name: zidovudine

Chemical Name: 3'-azido-3'-deoxythymidine

Molecular formula and molecular weight: $C_{10}H_{13}N_5O_4$ 267.24

Structural Formula:



Physicochemical properties:

Description: Zidovudine is a white to beige, odorless, crystalline solid. It has a melting point of 122-124°C and a solubility in water of 20.1 g/mL at 25°C.

pKa and pH: The pH value of a 10 mg/L solution of zidovudine in water is approximately 6.2. The pKa is 9.68.

Distribution Coefficient: The distribution coefficient of zidovudine between 1-octanol and distilled water at 25°C is 1.15.

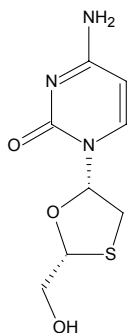
Drug Substance

Proper Name: lamivudine

Chemical Name: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2R-cis)-

Molecular formula and molecular weight: $C_8H_{11}N_3O_3S$ 229.3

Structural Formula:



Physicochemical properties:

Description:

Lamivudine is a white to off-white crystalline solid. It has a melting point of 176°C and a solubility of approximately 70 mg/mL in water at 20°C.

pKa and pH:

The pH value of a 1% w/v solution of lamivudine in water is approximately 6.9. The pKa determined by UV is 4.30.

Distribution Coefficient:

The distribution coefficient of lamivudine between octanol and water at pH 7.4 was -0.7 ± 0.2 when measured by HPLC.

Drug Substance

Proper Name:

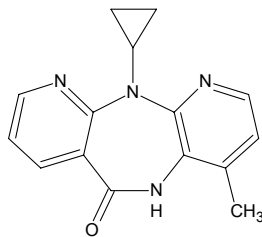
nevirapine

Chemical Name:

11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

Molecular formula and molecular weight: C₁₅H₁₄N₄O 266.30

Structural Formula:



Physicochemical properties:

Description: Nevirapine is a white to off-white, crystalline powder.

Solubility (mg/mL @ 25°C):

water	0.1
ethanol	5.5
methanol	8.1
chloroform	100.0
cyclohexane	0.01
hexane	0.001
40% propylene glycol/water	1.0

pKa and pH: pKa₁ = 2.8; pKa₂ = -0.4

Partition Coefficient: log K_{ow} = 1.8

Melting point: ~245°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed on healthy male volunteers under fasting conditions. The rate and extent of absorption of zidovudine, lamivudine and nevirapine was measured and compared following a single oral dose of Apo-TriAvir (zidovudine, lamivudine and nevirapine) or RETROVIR[®] (AZT[™]) (zidovudine) 3 x 100 mg capsules, 3TC[®] (lamivudine) 150 mg tablets and VIRAMUNE[®] (nevirapine) 200 mg tablets. The results from measured data are summarized in Tables 11, 12 and 13.

Table 11:

Summary Table of the Comparative Bioavailability Data Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg (A single oral dose of lamivudine 150 mg / zidovudine 300 mg / nevirapine 200 mg) Lamivudine 150 mg From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	Apo-Combination of Lamivudine/Zidovudine/ Nevirapine [†]	Co-administration of 3TC [®] /Retrovir [®] (AZT [™])/ Viramune [®] ^{††}	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUC _t (ng•h/mL)	6151.72 6289.96 (23)	6201.47 6301.57 (20)	99.2	93.3 – 105.4
AUC _{inf} (ng•h/mL)	6238.02 6375.64 (23)	6312.38 6412.51 (20)	98.8	93.1 – 104.9
C _{max} (ng/mL)	1539.56 1606.82 (30)	1627.37 1648.73 (18)	94.6	85.4 – 104.8
T _{max} [#] (h)	0.99 (30)	0.89 (46)		
T _{half} [#] (h)	5.11 (26)	6.86 (90)		
[#] Arithmetic means (CV%). ^{##} Based on the least squares estimate. [†] Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg [Aptex Inc.] ^{††} 3TC [®] Tablets, 150 mg [GlaxoSmithKline Shire BioChem]/ Retrovir [®] (AZT [™]) Capsules, 100 mg [GlaxoSmithKline Inc.]/ Viramune [®] Tablets, 200 mg [Boehringer Ingelheim] and was purchased in Canada.				

Table 12:

Summary Table of the Comparative Bioavailability Data Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg (A single oral dose of lamivudine 150 mg / zidovudine 300 mg / nevirapine 200 mg) Nevirapine 200 mg From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	Apo-Combination of Lamivudine/Zidovudine/ Nevirapine [†]	Co-administration of 3TC®/Retrovir® (AZT™)/ Viramune® ^{††}	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUC ₇₂ (ng•h/mL)	82492.2 83336.2 (14)	82807.8 83834.3 (14)	99.6	98.2 – 101.0
AUC _{inf} (ng•h/mL)	144075.8 153292.1 (42)	150011.6 157371.8 (34)	96.0	90.9 – 101.4
C _{max} (ng/mL)	2477.5 2505.3 (16)	2226.2 2256.5 (16)	111.3	106.7 – 116.0
T _{max} [#] (h)	1.93 (54)	2.27 (56)		
T _{half} [#] (h)	61.97 (48)	64.41 (38)		
# Arithmetic means (CV%).				
## Based on the least squares estimate.				
† Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg [Apotex Inc.]				
†† 3TC® Tablets, 150 mg [GlaxoSmithKline Shire BioChem]/ Retrovir® (AZT™) Capsules, 100 mg [GlaxoSmithKline Inc.]/ Viramune® Tablets, 200 mg [Boehringer Ingelheim] and was purchased in Canada.				

Table 13:

Summary Table of the Comparative Bioavailability Data Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg (A single oral dose of lamivudine 150 mg / zidovudine 300 mg / nevirapine 200 mg) Zidovudine 300 mg From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	Apo-Combination of Lamivudine/Zidovudine/ Nevirapine [†]	Co-administration of 3TC®/Retrovir® (AZT™)/ Viramune® ^{††}	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUC _t (ng•h/mL)	2809.03 2890.74 (29)	2927.70 3004.74 (23)	95.9	91.1 – 101.0
AUC _{inf} (ng•h/mL)	2843.60 2926.47 (29)	2961.32 3039.89 (23)	96.0	91.2 – 101.1
C _{max} (ng/mL)	2348.24 2476.90 (37)	2834.95 2963.19 (31)	82.8	73.2 – 93.7
T _{max} [#] (h)	0.46 (32)	0.49 (37)		
T _{half} [#] (h)	1.42 (12)	1.42 (10)		
# Arithmetic means (CV%).				
## Based on the least squares estimate.				
† Fixed Dose Combination of Lamivudine/Zidovudine/Nevirapine Tablets, 150 mg/300 mg/ 200 mg [Apotex Inc.]				
†† 3TC® Tablets, 150 mg [GlaxoSmithKline Shire BioChem]/ Retrovir® (AZT™) Capsules, 100 mg [GlaxoSmithKline Inc.]/ Viramune® Tablets, 200 mg [Boehringer Ingelheim] and was purchased in Canada.				

DETAILED PHARMACOLOGY

Pharmacokinetics in Adults

The single-dose pharmacokinetic properties of lamivudine and zidovudine have been studied in 24 healthy adult subjects in a single-center, open-label, randomized, three-way crossover study to evaluate the bioequivalence between lamivudine/zidovudine combination and the 150 mg lamivudine tablet and the 300 mg zidovudine tablet given simultaneously. The effect of food (67 grams fat, 33 grams protein, and 58 grams carbohydrate) on the rate and extent of absorption of lamivudine/zidovudine combination was also evaluated (see **Effect of Food on Absorption**). Lamivudine/zidovudine combination was bioequivalent to one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) when administered to fasting subjects.

The pharmacokinetics of nevirapine have been studied in nine Phase I studies and two Phase IIA studies in both HIV-1 infected adults (n=380) and healthy adult volunteers (n=119) given single doses of up to 400 mg and multiple doses of up to 600 mg/day (given q.d. or b.i.d.). (See **Part I, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**)

Nevirapine Clinical Studies

Trial BI 1090 (patients with advanced HIV disease, with or without prior antiretroviral treatment)

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 adult patients with <200 CD4+ cells at screening. More than 75% of patients had extensive prior treatment with monotherapy or dual therapy prior to entering the trial. Treatment in this trial reflected the pre-HAART era of standard of care. BI 1090 compared treatment with nevirapine + lamivudine versus placebo + lamivudine in NNRTI naïve patients, who were also taking other background antiretroviral agents. Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily, or placebo; lamivudine 150 mg twice daily; other antiretroviral agents were given at standard doses. The patients (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV infection, with a median baseline CD4+ cell count of 96 cells/mm³ and a baseline HIV RNA of 4.58 log₁₀ copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. There was no maximum limit to the duration of prior antiretroviral treatment. The 24% of patients who were permanently lost to follow-up during the study are included in the intent to treat (ITT) evaluations of virologic outcome. Patients were classified as responders at 48 weeks if their viral load decreased and remained below the limit of quantification (LOQ=50 copies/mL) by 48 weeks. Patients were categorized as non-responders if they did not complete 48 weeks, changed or added additional antiretroviral therapy, or experienced an AIDS defining event prior to 48 weeks. The virologic responder rate at 48 weeks was significantly higher for nevirapine patients (19%) than for placebo patients (3%).

Of the 2249 patients, 527 (23.4%) entered the trial as treatment naïve or having received only ZDV prior to entering the trial. The patients had advanced HIV-infection with a median CD4+ cell count of 91 cells/mm³ and baseline HIV RNA of 5.02 log₁₀ copies/mL (105,213 copies/mL). The virologic responder rates at 48 weeks were significantly higher for the nevirapine patients (40%) than the placebo patients (3%).

The change from baseline in CD4+ count through one year of therapy was significantly greater for the nevirapine group compared to the placebo group for the overall study population (64 cells/mm³ vs 22 cells/mm³, respectively). This was also evident for patients who entered the trial as first HAART (treatment naïve or having received only ZDV); the change from baseline in CD4+ count was significantly greater for the nevirapine group over placebo (85 cells/mm³ vs 25 cells/mm³, respectively).

Using an endpoint of the time to first new AIDS disease event or death in an intent to treat analysis in the overall study population, there was a 28% improvement in event-free survival in the nevirapine group compared to the placebo group (Risk ratio: 1.28; 95% confidence interval: 1.03 to 1.58).

INCAS (BI Trial 1046 – Adult Antiretroviral Naïve Patients)

INCAS (BI Trial 1046) compared treatment with nevirapine+ZDV+ddl versus ZDV+ddl versus nevirapine +ZDV in 151 HIV-1-infected patients (median age 36 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200-600 cells/mm³ (median 370 cells/mm³) and a mean baseline plasma HIV-1 RNA concentration of 4.41 log₁₀ copies/mL (25,704 copies/mL). Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily, or placebo; ZDV, 200 mg three times daily; ddl, 125 or 200 mg twice daily.

Using an intent to treat evaluation of virologic outcome, patients were classified as responders at 48 weeks if their viral load decreased and remained below LOQ (400 copies/mL) by 48 weeks. Patients were categorized as non-responders if they did not complete 48 weeks, changed or added additional antiretroviral therapy, or experienced an AIDS defining event prior to 48 weeks. The virologic responder rates at 48 weeks were significantly higher for nevirapine+ZDV+ddl patients (45%) compared to either the ZDV+ddl (19%) or nevirapine +ZDV patients (0%).

CD4+ cell counts in the nevirapine+ZDV+ddl group increased above baseline by a mean of 139 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in the ZDV+ddl patients. The nevirapine +ZDV group mean decreased by 6 cells/mm³ below baseline.

Absorption and Bioavailability

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the tablet and 87% ± 13% for the oral solution. After oral dosing (capsules) zidovudine was rapidly absorbed from the gastrointestinal tract. As a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 64% ± 10% (mean ± SD).

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 ± 9% (mean ± SD) for the 50 mg tablet and 91.8% for the oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 µg/mL are 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 µg/mL (17 ± 7µM), (n=242) were attained at 400 mg/day.

When nevirapine (200 mg) was administered to 24 healthy adults (12 male, 12 female), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 39 mL), 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 ddl, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or ddl.

Distribution

Lamivudine apparent volume of distribution after intravenous (IV) administration 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 $\mu\text{g/mL}$, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration. Similar to lamivudine, zidovudine apparent volume of distribution after IV administration was 1.6 L/kg and plasma protein binding is 34% to 38%.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF lamivudine concentrations in eight patients ranged from 5.6% to 30.9% (mean \pm SD of $14.2\% \pm 7.9\%$) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.30 $\mu\text{g/mL}$. The zidovudine CSF/plasma concentration ratio was determined in 39 adult patients receiving chronic therapy with zidovudine. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of zidovudine was 0.6 (range 0.04 to 2.62).

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier. Following intravenous administration in healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine also is widely distributed in humans. Nevirapine is approximately 57-61% 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

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral lamivudine dose in six 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.

Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-O- β -Dglucopyranuronosylthymidine (GZDV) which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recovery of zidovudine and GZDV accounted for 14% and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63% to 95%), indicating a high degree of absorption. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous administration of

zidovudine. AMT area-under-the-curve (AUC) was one-fifth of the AUC of zidovudine and had a half-life of 2.7 ± 0.7 hours. In comparison, GZDV AUC was about three-fold greater than the AUC of zidovudine.

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed *via* cytochrome P-450 (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 isozymes from the CYP3A family, 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 b.i.d. followed by a single 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 P-450 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 of nevirapine plays a minor role in elimination of the parent compound.

Elimination

Zidovudine pharmacokinetic data following intravenous dosing indicated dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1.6 L/hr/kg. Renal clearance is estimated to be 0.34 L/hr/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

The majority of lamivudine is eliminated unchanged in urine. In 20 patients given a single IV dose, renal clearance was 0.22 ± 0.06 L/hr/kg (mean \pm SD), representing $71\% \pm 16\%$ (mean \pm SD) of total lamivudine clearance. In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. Oral clearance was 0.37 ± 0.05 L/hr/kg (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. Renal clearance is estimated to be 314 mL/min, indicating glomerular filtration and active tubular secretion by the kidneys.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes in both animals and humans. The pharmacokinetics of autoinduction are characterized by an approximately 1.5- to 2-fold increase in systemic 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. The pharmacokinetics of nevirapine in the dose range of 200-400 mg/day remain approximately linear following autoinduction.

Special Populations

Impaired Renal Function

The elimination of lamivudine and zidovudine in patients with impaired renal function is diminished. Reduction of the dosages of lamivudine and zidovudine are recommended for patients with impaired renal function (see **WARNINGS AND PRECAUTIONS** section). The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 14.

Table 14: Pharmacokinetic Parameters (Mean \pm S.D.) After a Single 300 mg Oral Dose of Lamivudine in Three Groups of Adults with Varying Degrees of Renal Function (CrCl > 60 mL/min, CrCl = 10-30 mL/min, and CrCl < 10 mL/min)

Number of subjects	6	4	6
Creatinine clearance criterion	> 60 mL/min	10-30 mL/min	< 10 mL/min
Creatinine clearance (mL/min)	111 \pm 14	28 \pm 8	6 \pm 2
C _{max} (μ g/mL)	2.6 \pm 0.5	3.6 \pm 0.8	5.8 \pm 1.2
AUC _{∞} (μ g·h/mL)	11.0 \pm 1.7	48.0 \pm 19	157 \pm 74
Cl/F (mL/min)	464 \pm 76	114 \pm 34	36 \pm 11

These results show increases in C_{max} and half-life with diminishing creatinine clearance. Apparent total clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with reduced creatinine clearance (see **DOSAGE AND ADMINISTRATION** section).

The pharmacokinetics of zidovudine has been evaluated in patients with impaired renal function following a single 200 mg oral dose. In 14 patients (mean creatinine clearance 18 \pm 2 mL/min), the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half-life in these patients was 8.0 hours (vs 0.9 hours for control) and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were evaluated in a multiple-dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6). Patients received escalating doses of zidovudine up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well-tolerated despite significantly elevated plasma levels of GZDV. Total body clearance after oral administration of zidovudine was approximately 50% of that reported in patients with normal renal function. The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe renal dysfunction. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced.

Nevirapine in Renal Dysfunction

The single-dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild (50 \leq creatinine clearance <80 mL/min), moderate (30 \leq creatinine clearance <50 mL/min) or severe renal dysfunction (creatinine clearance <30 mL/min), renal impairment or end-stage

renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (creatinine clearance >80 mL/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43.5 % reduction in nevirapine AUC over a one-week exposure period. There was also accumulation of nevirapine hydroxy-metabolites in plasma. In renal dysfunction, a single-dose study suggested that patients with creatinine clearance ≥ 20 mL/min do not require an adjustment in nevirapine dosing.

Nevirapine in Hepatic Dysfunction

The single-dose pharmacokinetics of nevirapine have been compared in 10 subjects with hepatic dysfunction and 8 subjects with normal hepatic function. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤ 7 , do not require an adjustment in nevirapine dosing. However, the pharmacokinetics of nevirapine in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation. Therefore caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction. Nevirapine should not be administered to patients with severe hepatic dysfunction.

Pregnancy

The pharmacokinetics of zidovudine has been studied in a Phase 1 study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in five pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see **DRUG INTERACTIONS** section).

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults.

Nursing Mothers

See **WARNINGS AND PRECAUTIONS: Nursing Mothers**.

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum.

After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients

Apo-TriAvir has not been studied in pediatric patients.

Zidovudine

The pharmacokinetics and bioavailability of zidovudine have been evaluated in 21 HIV-infected

children, aged 6 months through 12 years, following intravenous doses administered over the range of 80 to 160 mg/m² every 6 hours, and following oral doses of the intravenous solution administered over the range of 90 to 240 mg/ m² every 6 hours. After discontinuation of the I.V. infusion, zidovudine plasma concentrations decayed biexponentially, consistent with two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine concentrations were observed with increasing dose, consistent with dose-independent kinetics over the dose range studied. The mean terminal half-life and total body clearance across all dose levels administered were 1.5 hours and 30.9 mL/min/kg, respectively. These values compare to mean half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min/kg.

The mean oral bioavailability of 65% was independent of dose. This value is the same as the bioavailability in adults. Doses of 180 mg/ m² four times daily in pediatric patients produced similar systemic exposure (24 hour AUC 10.7 hr•µg/mL) as doses of 200 mg six times daily in adult patients (10.9 hr•µg/mL).

The pharmacokinetics of zidovudine has been studied in neonates from birth to 3 months of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of pregnancy, zidovudine elimination was determined immediately after birth in 8 infants who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In another study, the pharmacokinetics of zidovudine was evaluated in infants (ranging in age of 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In infants less than or equal to 14 days old, mean ± SD total body clearance was 10.9 ± 4.8 mL/min/kg (n=18) and half-life was 3.1 ± 1.2 hours (n=21). In infants greater than 14 days, total body clearance was 19.0 ± 4.0 mL/min/kg (n=16) and half-life was 1.9 ± 0.7 hours (n=18). Bioavailability was 89% ± 19% (n=15) in the younger age group and decreased to 61% ± 19% (n=17) in infants older than 14 days.

Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and I.V. drug administration in 21 children during Phase I and Phase II studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours post-dose at doses of 120 to 240 mg/ m² was 0.52 ± 0.44 (n=28); after an I.V. infusion of doses of 80 to 160 mg/ m² over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n=23) at 3.2 hours after the start of the infusion. During continuous intravenous infusion the mean steady-state CSF/plasma ratio was 0.26 ± 0.17 (n=28).

As in adult patients, the major route of elimination in children was by metabolism to GZDV. After I.V. dosing, about 29% of the dose was excreted in the urine unchanged and about 45% of the dose was excreted as GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients older than 3 months of age is similar to that of zidovudine in adult patients.

Lamivudine

Pharmacokinetic properties of lamivudine have been assessed as part of a study of 97 HIV-infected patients. A subset of 57 of these patients had pharmacokinetic assessments after oral and IV administration of 1, 2, 5, 8, 12 and 20 mg/kg per day. These patients ranged in age from 4.8 months to 16 years and in weight from 5 to 66 kg. In the 9 infants and children receiving 8 mg/kg per day, absolute bioavailability was 66% ± 26% (mean ± S.D.), which is less than the

86% ± 16% (mean ± S.D.) observed in adolescents and adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

After oral administration of 8 mg/kg of lamivudine to 12 pediatric patients, C_{max} was 1.2 ± 0.5 µg/mL and half-life was 2.1 ± 0.6 hours (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.). There were no significant differences in pharmacokinetic properties in infants compared with children. There were no significant differences in $T_{1/2}$ across the range of doses. AUC and C_{max} increased in proportion to dose over the range from 1 to 20 mg/kg. Total exposure to lamivudine, as reflected by AUC, was comparable between pediatric patients receiving an 8 mg/kg dose and adults receiving a 4 mg/kg dose.

Distribution of lamivudine into cerebrospinal fluid was assessed in 38 pediatric patients. Cerebrospinal fluid concentrations were 3% to 47% of the concentration in a simultaneous serum sample.

Nevirapine

Safety and effectiveness of nevirapine in HIV-1 infected pediatric patients younger than 15 years of age has not been established.

Geriatric Patients

Lamivudine and zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Nevirapine pharmacokinetics in HIV-1-infected adult males and females do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

Gender

There are no significant differences in pharmacokinetic properties of lamivudine by gender.

In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (V_{dss}/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), ($p=0.001$, Wilcoxon rank sum test) suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance or plasma concentrations following either single- or multiple-dose administration(s). Furthermore, an evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (37 females, 205 males) revealed no clinically significant difference in nevirapine steady-state trough concentrations (median $C_{minss} = 4.6$ µg/mL females, 4.2 µg/mL males) with long-term nevirapine treatment at 400 mg/day.

Race

There are no significant differences in pharmacokinetic properties of lamivudine among races.

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median $C_{\text{minss}} = 4.7 \mu\text{g/mL}$ Black, $3.8 \mu\text{g/mL}$ Hispanic, $4.3 \mu\text{g/mL}$ Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Effect of Food on Absorption

The extent of lamivudine and zidovudine absorption (AUC_{∞}) and estimates of half-life following administration of lamivudine/zidovudine combination with food were similar when compared to fasting subjects. Therefore, Apo-TriAvir may be administered with or without food. The rate of absorption (C_{max} , t_{max}) was slowed by food. Lamivudine C_{max} and zidovudine C_{max} were decreased by 15% (4% to 24%) and 45% (35% to 54%) (geometric mean ratio with 90% confidence interval), respectively, when administered with food. The slower rate of absorption in the presence of food resulted in a median prolongation of t_{max} , approximately 0.9 hours for lamivudine and 0.6 hours for zidovudine, when compared to fasted conditions.

MICROBIOLOGY

Virology

Lamivudine and zidovudine are potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, lamivudine and zidovudine are phosphorylated to their active 5-triphosphate metabolites, lamivudine triphosphate (L-TP) and zidovudine triphosphate (ZDV-TP). *In vitro* L-TP and ZDV-TP have an intracellular half-life of approximately 10.5 to 15.5 hours and 3 hours respectively. The principal mode of action of L-TP and ZDV-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP inhibits is a weak inhibitor of mammalian α , β , and γ -DNA polymerases. ZDV-TP is a weak inhibitor of the cellular DNA polymerase- α and mitochondrial polymerase- γ and has been reported to be incorporated into the DNA of cells in culture.

Nevirapine is a non-nucleoside RT inhibitor, which exhibits selective antiviral activity against HIV-1. Nevirapine inhibits the replication of a wide variety of HIV-1 strains in a number of cellular assays. The relationship between *in vitro* susceptibility of HIV-1 to nevirapine and the inhibition of HIV-1 replication in humans has not been established. The *in vitro* antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC_{50} values (50% inhibitory concentration) ranged from 10-100 nM against laboratory clinical isolates of HIV-1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV in drug combination regimens with zidovudine (ZDV), didanosine (ddl), stavudine (d4T), lamivudine (3TC) and saquinavir (SQV) and indinavir. HIV-1 isolates exhibiting reduced susceptibility to nevirapine were selected in cell culture experiments and during *in vivo* clinical studies.

In Vitro Activity

The relationships between *in vitro* susceptibility of HIV to lamivudine and zidovudine and the inhibition of HIV replication in humans or clinical response are still being investigated. The anti-

HIV activity of nucleoside analogues *in vitro* can vary depending on the viral strain, cell type, and assay used to measure such activity. To assess the activity of lamivudine and zidovudine, a number of virus/cell combinations were used, and inhibitory activity was measured in different assays by determination of IC₅₀ and IC₉₀ values. Lamivudine and zidovudine demonstrated anti-HIV-1 activities in all virus/cell combinations tested. However, zidovudine activity was substantially less in chronically infected cell lines.

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds (zidovudine, zalcitabine, and didanosine) using HIV-1-infected MT-4 cells as the test system. The MTT formazan assay demonstrated synergistic antiretroviral activity between lamivudine and zidovudine, additive antiretroviral activity between lamivudine and zalcitabine, and additive antiretroviral activity between lamivudine and didanosine. The combination of lamivudine/zidovudine also showed synergistic activity in a variable-ratio study.

Resistance

In nonclinical studies, lamivudine-resistant isolates of HIV have been selected *in vitro*. A known mechanism of lamivudine resistance is the change in the 184 amino acid of RT from methionine to either isoleucine or valine. *In vitro* studies indicate that zidovudine-resistant viral isolates can become sensitive to zidovudine when they acquire the 184 mutation. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a < 4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown.

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

In vitro resistance to zidovudine is due to the accumulation of specific mutations in the HIV reverse transcriptase coding region. Six amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, L210W, Thr215→Tyr or Phe, and Lys219→Gln) have been described in viruses with decreased *in vitro* susceptibility to zidovudine inhibition. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by accumulation of at least four to six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for subsequent use of any other approved reverse transcriptase inhibitors.

For isolates collected in clinical studies, phenotypic and genotypic resistance data showed that resistance to lamivudine monotherapy or combination therapy with lamivudine plus zidovudine developed in most patients within 12 weeks. Evidence in isolates from antiretroviral-naïve patients suggests that the combination of lamivudine and zidovudine delays the emergence of mutations conferring resistance to zidovudine. Combination therapy with lamivudine plus

zidovudine did not prevent phenotypic resistance to lamivudine. However, phenotypic resistance to lamivudine did not limit the antiretroviral activity of combination therapy with lamivudine plus zidovudine. In antiretroviral therapy-naïve patients, phenotypic resistance to lamivudine emerged more slowly on combination therapy than on lamivudine monotherapy. In the zidovudine-experienced patients on lamivudine plus zidovudine, no consistent pattern of changes in phenotypic resistance to lamivudine or zidovudine was observed.

HIV isolates with reduced susceptibility (100-250 fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV RT gene at amino acid positions 181 and/or 106 depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NRTI's.

Phenotypic or genotypic changes in HIV-1 isolates from patients treated with either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1 or \geq 12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro*; one or more of the RT mutations at amino acid positions 103, 106, 108, 181, 188, and 190 were detected in some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV isolates with a >100 fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations; 19 of 24 patients (80%) had isolates with a position 181 mutation regardless of dose. Nevirapine + ZDV combination therapy did not alter the emergence rate of nevirapine-resistant virus or the magnitude of nevirapine resistance *in vitro*; however, a different RT mutation pattern, predominantly distributed amongst amino acid positions 103, 106, 188, and 190, was observed. In patients (6 of 14) whose baseline isolates possessed a wild type RT gene, nevirapine+ZDV combination therapy did not appear to delay emergence of ZDV-resistant RT mutations.

Genotypic and phenotypic resistance was examined for patients receiving nevirapine in triple and double therapy drug combination therapy, and in the non-nevirapine comparative group from the phase II INCAS study. Antiretroviral naïve subjects with CD4 cells counts of 200-600/mm³ were treated with either nevirapine + ZDV (n=46), ZDV + ddI (n=51) or nevirapine + ZDV + ddI (n=51) and followed for 52 weeks or longer on therapy. At 24 weeks, all available isolates (32/32) recoverable from patients receiving nevirapine as part of a two or three drug combination were resistant to this agent, while 18/21 (86%) patients carried such isolates at 30-60 weeks. With respect to genotypic NVP resistance, in 12 isolates from 11 patients receiving triple therapy, the most common single mutation was K103N, followed by G190A and Y181C.

The prevalence of phenotypic drug resistance was assessed in 60 patients with a viral rebound after they received a protease inhibitor (PI) or nevirapine containing regimen. Resistance testing was done within 36 weeks of viral rebound classified as a subsequent increase to >500 copies/mL following an initial viral load decrease to <500 copies/mL or a viral rebound of ≥ 0.5 log₁₀ following an initial drop of ≥ 1.0 log₁₀. In total, 88.9% given nevirapine had strains with reduced susceptibility to the drug. Overall, 46 patients (76.7%) harboured a strain resistant to ≥ 1 drug of their initial PI or nevirapine containing regimen. Of 53 patients who remained on treatment at the time of the study (40 had switched to a different combination from that at

baseline), 6 harboured isolates susceptible to all drugs they had ever received.

The clinical relevance of phenotypic and genotypic changes associated with nevirapine therapy has not been established.

Cross-Resistance

The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥ 1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr and Gln151→Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine. A second pattern, typically involving a T69S mutation plus a 6 base-pair inserted at the same position, results in a phenotypic resistance to zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Rapid emergence of HIV strains which are cross-resistant to NNRTI's has been observed *in vitro*. Data on cross-resistance between the NNRTI nevirapine and nucleoside analogue RT inhibitors are very limited. In four patients, ZDV-resistant isolates tested *in vitro* retained susceptibility to nevirapine and in six patients, nevirapine-resistant isolates were susceptible to ZDV and ddI. One case of double resistance to ZDV and nevirapine including transmission has been reported.

Cross-resistance between nevirapine and HIV protease inhibitors is unlikely because the enzyme targets involved are different.

Cross-resistance among the currently registered NNRTIs is broad. Some genotypic resistance data indicate that in most patients failing NNRTIs, viral strains express cross-resistance to the other NNRTIs. The currently available data do not support sequential use of NNRTIs.

Cytotoxicity

The results of cytotoxicity studies in various assays have shown little cytotoxic action with lamivudine. Cytotoxicity of lamivudine was compared with that of zidovudine, zalcitabine, and didanosine in four T-lymphoblastoid cell lines; one monocyte/macrophage-like cell line; one B-lymphoblastoid cell line; and peripheral blood lymphocytes (PBLs) using both cell proliferation (CP) and [3H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [3H]-thymidine uptake results demonstrated a similar trend to those from the CP assays. Lamivudine had no cytotoxic effect when incubated for 10 days with phytohemagglutinin (PHA)-activated human lymphocytes or human macrophages.

The cytotoxicity of combinations of lamivudine with zidovudine, zalcitabine, or didanosine was evaluated in PHA-activated PBLs and CEM cells by measuring cellular uptake of [3H]-

thymidine. Lamivudine greatly reduced the cytotoxicity of zalcitabine, slightly reduced the cytotoxicity of zidovudine in some cases, and did not alter the cytotoxicity of didanosine.

In myelotoxicity studies *in vitro*, lamivudine demonstrated no toxic effects against erythroid, granulocyte-macrophage, pluripotent, or stromal progenitor cells from healthy human donors. Lamivudine was not toxic to human hematopoietic supportive stroma, nonadherent hematopoietic cells, or stromal fibroblasts and produced minimal changes in cytokine (GM-CSF) production from mitogen-stimulated bone marrow stromal cells. Lamivudine was less toxic than zidovudine, zalcitabine, ara-C, 3FT, and stavudine in these studies. In another study, lamivudine was not toxic to activated human T-cells.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth inhibition assay. ID₅₀ values for several human cell lines showed little growth inhibition by zidovudine except at concentrations >50 µg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID₅₀ of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID₅₀ value of <1.25 µg/mL was estimated. Two of 10 human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 µg/mL or less.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies with lamivudine and zidovudine have been performed in the mouse and rat. The acute oral administration of very high doses of lamivudine (two doses of 2000 mg/kg) in mice was associated with transient increases in sexual activity in males and general activity in males and females. There were no deaths and no evidence of target organ toxicity. Therefore the maximum non-lethal oral dose of lamivudine in mice is greater than two doses of 2000 mg/kg.

The acute intravenous administration of lamivudine at 2000 mg/kg was well tolerated by both mice and rats and was not associated with any target organ toxicity. A number of non-specific clinical signs were observed which were more severe in rats but were all of relatively short duration.

Acute toxicity studies with zidovudine in mice and rats at doses up to 750 mg/kg produced only one death, in a mouse given 487 mg/kg of zidovudine. Death was preceded by chronic convulsions. Decreased activity, ptosis and laboured breathing were noted in other animals for up to 35 minutes post-dose. No effects were seen during the 14-day post-dose observation period.

In a second set of acute toxicity studies at higher doses of zidovudine, the median lethal doses for mice were 3568 mg/kg and 3062 mg/kg for male and female, respectively. In rats, the median lethal doses were 3084 mg/kg for males and 3683 mg/kg for females.

Clinical signs noted prior to death included ptosis, decreased activity, ataxia, body tremors, urine stains and prostration in mice. In rats, decreased activity and salivation occurred in most animals; the males receiving 5000 mg/kg also exhibited rough coats and lacrimation.

Acute oral toxicity studies conducted in the mouse, rat, dog, and monkey revealed that the NOEL was 200 mg/kg, and lethality did not occur in any of these species with single PO doses ranging from 50 to 400 mg/kg. These studies indicated that the species sensitivity was (in order of decreasing sensitivity): rat > dog > mouse > monkey. Subchronic non-clinical NOELs ranged from 5 to <650 mg/kg/day, in mice, rats, and dogs. Maximum tolerated dose (MTD) ranged from 25 to 1500 mg/kg/day in the same species. Chronic studies in the rat and dog indicated that the liver and haematopoietic system are amongst the target organs, with NOELs of 5.50 mg/kg/day and MTDs of 50-200 mg/kg/day.

Long-Term Toxicity

In repeat dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2000 mg/kg b.i.d. for 6 months. Treatment-related effects were restricted to minor haematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and the mucosal hyperplasia of the caecum (in the 6 month study). The no (toxicologically important) effect level was 450 mg/kg b.i.d.

In the dog, oral doses of lamivudine 1500 mg/kg b.i.d. in males and 1000 mg/kg b.i.d. in females for a period of 12 months were well tolerated. Treatment-related changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high dose animals, but with no effect on bone marrow cytology. Deaths were seen in females dosed with 1500 mg/kg b.i.d. in a 3 month study but not in a 12 month study, using a dose of 1000 mg/kg b.i.d.

When administered orally for one month, at a dose of 1000 mg/kg b.i.d., lamivudine demonstrated low haematotoxic potential in the mouse, and did not significantly enhance the haematotoxicity of zidovudine or interferon α .

The results of long-term toxicity studies with zidovudine in rats, dogs and monkeys are presented in the table below. Rats and monkeys received zidovudine by gavage, dogs were administered zidovudine capsules.

Table 15: Long-term Toxicity Studies with Zidovudine in Rats, Dogs and Monkeys.

Species	No. per Group		Dose Levels (mg/kg/day)	Duration (weeks)	Effects
	M	F			
CD Rat	5	5	0, 60, 125, 250, 500	2	Post-dose salivation. Weight loss in mid-dose (1/5) and high-dose (1/5) males.
CD Rat	12	12	0, 56, 167, 500	13	Anogenital staining in high-dose rats. Increased blood glucose levels in high-dose females at term. Occasional decreases in SGOT in both sexes at high dose.
CD Rat	25	25	0,50, 150, 450	52	Salivation at high dose for the first 4 weeks. Moderate, reversible macrocytic anemia, with

					reticulocytosis, in the high-dose animals. Increased urine output in some high dose animals.
Dog	1	1	0, 125, 250, 500	2	High-dose female sacrificed day 14, following 2 days emesis. High-dose male had bloody vomitus on days 11, 14, 16. Marked leukopenia and thrombocytopenia in all treated dogs, most severe in high-dose. Alk. phos., BUN and creatinine increased in high-dose female. Slight increase in kidney weight in both high-dose dogs and in mid-dose male. Focal to diffuse hemorrhage in GI tract and mesentery of both high-dose dogs and mid-dose female. Moderate hypoactivity in the lymph nodes, involution of the thymus (mid- and high-dose females, high-dose male) and splenic lymphoid atrophy (high-dose male only). Dose-related mild to marked hypocellularity of the bone marrow at all dose levels.
Monkey (Cynomolgus)	1	1	0, 125, 250, 500	2	Emesis in high-dose male. Decreased RBC, hematocrit and hemoglobin in all groups (all values within normal range). Increased SGPT in mid- and high-dose males, more marked in high-dose females.
Monkey (Cynomolgus)	4	4	0, 34, 100, 300	13	Emesis in one high-dose male. Mild to moderate decrease in RBC, HCT and HB; slight to mild increase in MCV in mid- and high-dose groups. Slight decrease in WBC in high-dose males.
Monkey (Cynomolgus)	5	5	0, 34, 100, 300	26	Decreased RBC, HCT and HB in all groups, generally doserelated. Increase in MCV and MCH more prominent in males. Dose-related retardation of bone marrow cell maturation, particularly in erythroid elements. Slight, inconsistent, increase in platelets in mid- and high-dose group.
Monkey (Cynomolgus)	6	6	Males-35, 100, 300 Females-35, 100, 300	52	Dose-related macrocytic anemia (i.e., decreased RBC, HCT and HB, increased MCV and MCH) maximized by week 26 at latest. After 4 weeks recovery, the bone marrow smears were similar in control and treated animals. The severity of anemia was similar to that in the 3-month and 6-month study.

Carcinogenicity and Mutagenicity

Lamivudine

Traditional 24 month carcinogenicity studies using lamivudine have been conducted in mice and rats at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at recommended therapeutic doses. The following results should be noted. In mice, there appeared to be an increased incidence of histiocytic sarcoma in female mice treated with 180 mg/kg/day (6 of 60 mice) and 2000 mg/kg/day (5 of 60 mice) when compared to control mice (two control groups with 1 of 60 and 2 of 60 mice). There did not appear an increased incidence in histiocytic sarcoma in females mice treated with 600 mg/kg/day (3 of 60 mice). It should be noted that the control incidence of this type of tumour in this strain of mice can be as high as 10% similar to that found in the 180 and 2000 mg/kg/day groups. In rats, there appeared to be an increased

incidence of endometrial epithelial tumours in female rats treated with 3000 mg/kg/day (5 of 55 rats) when compared to control rats (two control groups each with 2 of 55 rats). There did not appear to be an increased incidence for endometrial tumours in rats treated with 1000 mg/kg/day (2 of 55 rats) or 300 mg/kg/day (1 of 55 rats). It should be noted that there did not appear to be an increased incidences of any proliferative non-neoplastic epithelial lesions in treated female rats when compared to control rats, and the incidence of adenocarcinoma (5/55 or 9%) was only slightly higher than recorded controls at the laboratory where the study was conducted (4/50 or 8%). The statistical significance of the findings in mice and rats varied with the statistical analysis conducted, and therefore, the statistical and hence, the clinical significance of these findings are uncertain. However, based on the similarity to historical control data, it was concluded that the results of long term carcinogenicity studies in mice and rats for lamivudine did not seem to show a carcinogenic potential relevant for humans.

Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons).

Zidovudine

Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg per day in mice and 80, 220, and 600 mg/kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg per day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on day 91 and then to 300 mg/kg per day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (five non-metastasizing squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumours were found at the lowest dose.

In rats, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumours occurred at the low or middle dose in rats. No other drug-related tumours were observed in either sex of either species.

At doses that produced tumours in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 8 times (mouse) and 57 times (rat) the estimated human exposure following a single dose of 300 mg.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in

incidence of vaginal tumours was noted with no increase in tumours in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumours in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay at concentrations up to 10 µg per plate, which was the maximum concentration that could be tested because of the antimicrobial activity of zidovudine against the *Salmonella* species. In a mutagenicity assay conducted in L5178Y/TK[±] mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4,000 and 5000 µg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1,000 µg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 µg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 µg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 µg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 µg/mL 5 minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine 100 to 1,000 mg/kg per day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg per day in rats and mice.

In a study involving 11 AIDS patients, it was reported that the seven patients who were receiving zidovudine (1,200 mg/day) as their only medication for 4 weeks to 7 months showed a chromosome breakage frequency of 8.29 ± 2.65 breaks per 100 peripheral lymphocytes. This was significantly ($p < 0.05$) higher than the incidence of 0.5 ± 0.29 breaks per 100 cells that was observed in the four AIDS patients who had not received zidovudine. A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The clinical significance of these findings is unknown.

Nevirapine

In carcinogenicity studies, nevirapine increased the incidence of liver tumours in mice (at doses up to 750 mg/kg/day). In a rat study, (at doses up to 35 mg/kg/day), benign adenomas occurred at doses less than the recommended human daily dose.

In genetic toxicology assays, nevirapine showed no evidence of mutagenic activity in a battery of *in vitro* and *in vivo* assays including microbial assays for gene mutation (Ames test in Salmonella strains and E. coli), mammalian cell gene mutation (HGRPT) assays in Chinese hamster ovary (CHO) cell line, cytogenetic assays using a CHO cell line and mouse bone marrow micronucleus assay following oral administration. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that observed following a human clinical dosage of 400 mg/day.

Reproduction and Teratology

Zidovudine

In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

In a fertility and reproduction study, male rats were dosed for 85 days prior to mating and females for 26 days prior to mating and throughout gestation and lactation. No fetal malformations or variations occurred, but the mid- and high-doses were both embryotoxic, increasing the number of early resorptions and decreasing litter sizes. No embryotoxic effects occurred in untreated females mated with treated males.

No evidence of teratogenicity was found in rats given oral doses of zidovudine of up to 500 mg/kg/day on days 6 through 15 of gestation. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats of 66 to 226 times the peak human plasma concentrations.

In a second teratology study in rats, an oral dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg/day) caused marked maternal toxicity and an increase in the incidence of fetal malformations including absent tail, anal atresia, fetal edema, situs inversus, diaphragmatic hernia, bent limb bones, atlas occipital defect and vertebral and/or rib anomalies. There was also a significant increase in the number of litters with bent ribs, reduced ossification of the vertebral arches, and presacral vertebrae. This dose resulted in peak zidovudine plasma concentrations 117 times peak human plasma concentrations. (Estimated area-under-the-curve AUC in rats at this dose level was 327 times the daily AUC in humans following a single dose of 300 mg). No evidence of teratogenicity was seen in the experiment at doses of 600 mg/kg/day or less.

In one of two studies in pregnant rabbits, the incidence of fetal resorptions was increased in rabbits given 500 mg/kg/day. There was no evidence of a teratogenic effect at any dose level. The doses used in these studies resulted in peak zidovudine plasma concentrations in rabbits of 5 to 49 times mean peak human plasma concentrations achieved following a single 300 mg. dose of zidovudine.

Peri- and Post-natal Studies

A separate peri- and post-natal study was conducted in pregnant rats given doses of 0, 50, 150 and 400 mg/kg/day from day 17 of gestation through to day 21 of lactation. There were no adverse effects noted in either generation. The reproductive capacity of those F₁ generation pups, which were raised to sexual maturity was not affected.

Neonatal animals were given 0, 80, 250 or 750 mg/kg/day for two months, starting on lactation day 8. Treatment-related alterations occurred only in the high-dose group and were reversible macrocytic anemia and increased urine output in both sexes, and decreased body weight gain in males. Mild to moderate increases in spleen weights were also noted.

Lamivudine

A range of studies has been performed to assess the effects of repeated oral administration of lamivudine upon mammalian reproduction and development.

In a rat fertility study, except for a few minor changes in high dose (2000 mg/kg b.i.d) animals, the overall reproductive performance of the F₀ and F₁ generation animals, and the development of the F₁ and F₂ generation, was unaffected by treatment with lamivudine.

Lamivudine was not teratogenic in the rat or rabbit, at doses up to 2000 mg/kg b.i.d. and 500 mg/kg b.i.d., respectively. In the rabbit a slight increase in the incidence of preimplantation loss at doses 20 mg/kg b.i.d. and above indicates a possible early embryolethal effect. There was no such effect in the rat. These marginal effects occurred at relatively low doses, which produced plasma levels comparable to those achieved in patients.

In a peri-/post-natal/juvenile toxicity study in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the caecum were observed in dams and pups at the high dose level. An increased incidence of urination upon handling was also seen in some offspring receiving 450 or 2000 mg/kg. In addition, a reduction in testes weight was observed in juvenile males at 2000 mg/kg which was associated with slight to moderate dilatation of the seminiferous tubules.

Nevirapine

There was no evidence of teratogenicity in reproductive studies performed in rats and rabbits treated with oral doses up to 50 and 300 mg/kg/day nevirapine. In rats a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended clinical dose. Maternal toxicity and observable effects on fetal development were not observed in the rat with a systemic exposure equivalent to that seen at the recommended human dose or in the rabbit with a systemic exposure approximately 50% higher than that seen at the recommended human dose.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

^{Pr}Apo-TriAvir

300 mg zidovudine, 150 mg of lamivudine and 200 mg nevirapine tablets

This leaflet is part III of a three-part “Product Monograph” published when Apo-TriAvir was approved for sale in Canada and is designed specifically for Consumers. Please read this leaflet carefully before you take Apo-TriAvir. This leaflet is a summary and will not tell you everything about Apo-TriAvir. Please do not throw away this leaflet until you have finished your medicine. You may need to read it again. Contact your doctor or pharmacist if you have any questions about the drugs contained in Apo-TriAvir.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is Apo-TriAvir (zidovudine, lamivudine and nevirapine). Apo-TriAvir is a treatment that contains a combination of three active ingredients that are currently available as separate medicines; zidovudine, lamivudine and nevirapine. Apo-TriAvir can only be obtained with a prescription from your doctor. You should not be taking zidovudine nor lamivudine nor nevirapine while taking Apo-TriAvir except during lead in dosing.

What it does:

The human immunodeficiency virus (HIV) is a retrovirus. Infection with HIV damages the immune system that can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

Apo-TriAvir is an antiretroviral medication. Apo-TriAvir does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down the production of new viruses.

When it should not be used:

Apo-TriAvir should not be used in patients with:

- previously demonstrated allergy to any of the components of the product (see **What the nonmedicinal ingredients are.**).
- abnormally low red blood cell count (e.g. anemia) or white blood cell count (e.g. neutropenia).
- if you have a severe liver problem
- if you weigh less 50 kg (110 lb.)

The coadministration of Apo-TriAvir with lamivudine or zidovudine or nevirapine is not recommended, except during lead in dosing.

What the medicinal ingredient is:

Each Apo-TriAvir tablet contains 300 mg of zidovudine 150 mg of lamivudine and 200 mg nevirapine.

What the nonmedicinal ingredients are:

Each Apo-TriAvir tablet also contains the non-medicinal ingredients microcrystalline cellulose, methylcellulose, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide.

What dosage forms it comes in:

Each Apo-TriAvir tablet contains 300 mg of zidovudine 150 mg of lamivudine and 200 mg nevirapine.

SERIOUS WARNINGS AND PRECAUTIONS

Liver Damage:

Severe, life-threatening, and in some cases fatal liver damage, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. Female gender and higher CD4 counts at the initiation of therapy place patients at increased risk of liver adverse events. Increased liver enzyme levels and/or co-infection with hepatitis B and C at the start of antiretroviral therapy are associated with a greater risk of liver adverse events (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**).

Skin Rash:

Severe, life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, occurring almost exclusively during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome characterized by rash and organ dysfunction (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**). Your doctor will monitor your condition during the first 18 weeks of treatment, and may stop treatment with Apo-TriAvir if severe skin rash or hypersensitivity reaction occurs.

High Levels of Acid in the Blood and Swollen Liver with Fatty Liver:

High levels of acid in the blood and swollen liver with fatty liver, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Your doctor will likely stop this treatment if high levels of acid in the blood or pronounced liver damage occurs (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**).

Post-Treatment Worsening of Hepatitis B:

Your doctor may test you for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Apo-TriAvir is not indicated for the treatment of chronic HBV infection and the safety and efficacy of Apo-TriAvir have not been established in patients co-infected with HBV and HIV. Worsening of hepatitis B has been reported in patients after the discontinuation of antiretroviral therapy. If you have both HIV and HBV your doctor will monitor your condition for at least several months after stopping treatment with Apo-TriAvir (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**).

BEFORE you use Apo-TriAvir talk to your doctor or pharmacist if:

- You ever had to stop taking this or another medication for this illness because you were allergic to them or they caused problems.
- You have any allergies to food or drugs.
- You had, or do you have, any diseases of the kidney.
- You had, or do you have, any diseases of the liver, particularly hepatitis B or C infection.
- You had, or do you have, very low red blood cell count (e.g. anemia) or very low white blood cell count (e.g. neutropenia).
- You are pregnant or intend to become pregnant.
- You are breast-feeding mother.
- You are taking any medications, including prescription, non-prescription, herbal or homeopathic.
- You are undergoing dialysis.

If your answer is **yes** to any of these questions, tell your doctor or pharmacist as soon as possible, if you have not already done so.

Remember that treatment with Apo-TriAvir does not reduce the risk of passing the infection onto others. You will still be able to pass HIV by sexual contact or by blood transfusion and you should use appropriate precautions.

While taking Apo-TriAvir or any other therapy for HIV disease, you may continue to develop other infections and other complications of HIV infection. Therefore, you should keep in regular contact with the doctor who is treating your condition.

Because your medicine helps to control your condition but does not cure it, you will need to take it every

day. Do not stop taking your medicine without first talking to your doctor.

It is important that your doctor knows about all your symptoms even if you think they are not related to HIV infection. Your doctor may need to change the dose of your medicine.

Use Of This Medicine During Pregnancy and Breast Feeding

If you are pregnant, or likely to become pregnant soon, or if you are breast feeding, please inform your doctor before taking any drugs, including Apo-TriAvir.

Babies and infants exposed to certain antiretroviral medications during pregnancy and labour, show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

There have been very rare reports of disease that affect the nervous system such as delayed development and seizures.

These findings do not affect the current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

It is recommended that HIV infected women do not breast feed their infants in order to avoid transmission of HIV. The active substances in Apo-TriAvir are found in human breast milk. Mothers taking Apo-TriAvir should not breast feed their infants.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies, including those you have bought yourself. Apo-TriAvir should not be taken with ribavirin, stavudine or zalcitabine.

Apo-TriAvir may change the effectiveness of oral contraceptives. Therefore oral contraceptives and other hormonal methods of birth control should not be used as a method of contraception.

Do not take ketoconazole or rifampin with Apo-Triavir.

Tell your doctor if you are taking clarithromycin, fluconazole, methadone or rifabutin.

It is recommended that you not take Apo-TriAvir with St. John's Wort, which can reduce the amount of nevirapine in your body.

PROPER USE OF THIS MEDICATION

Usual dose:

Take your medicine as your doctor has advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist. Do not change the dose without consulting your doctor.

This medicine is for you. Never give it to someone else, as it may harm them even if their symptoms are the same as yours.

Adults and Adolescents (at least 15 years old):

- Initial dose: As a general guide, swallow 1 tablet once a day for the first 14 days with or without food. This reduces the frequency of a rash developing. If a rash develops or you have signs of liver problems (see **SIDE EFFECTS**) then see your doctor and do not start regular dosing.
- Regular dose: Then take 1 tablet twice daily.

Patients who interrupt Apo-TriAvir for more than 7 days, should see your doctor at once regarding lead-in dosing.

Overdose:

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should **immediately** contact either your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:

Patients who miss a dose should take it as soon as they remember and then continue as before. Do not double the next dosage.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Patients may develop severe liver disease or skin reactions that can cause death. The risk of these

reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later. Your doctor should check you and do liver function tests (blood tests) often in the first 18 weeks of therapy. Checks for liver problems should continue during your therapy. Patients with higher liver function tests and patients with hepatitis B or C have a greater chance of liver damage while taking nevirapine, a component of Apo-TriAvir. Women and patients with higher CD4 counts seem to have a greater chance of developing liver damage, often accompanied by a rash, while taking nevirapine.

Women with higher CD4 counts are at the greatest risk of these events. If you are a woman with CD4 > 250 cells/mm³ or a man with CD4 > 400 cells/mm³ you should not begin taking Apo-TriAvir unless you and your doctor have decided that the benefit of doing so outweighs the risk. It is important that you attend all visits as scheduled by your doctor to monitor your health. It is important to remain under the care of a doctor while taking Apo-TriAvir.

In rare cases liver problems have led to liver failure, which can lead to liver transplants or death. Therefore, if you develop any of the following symptoms of liver problems, you must stop taking the medicine and tell your doctor immediately.

- general ill feeling or “flu-like” symptoms
- tiredness
- dark urine
- pale stool (bowel movements)
- nausea (feeling sick to your stomach)
- lack of appetite
- pain, ache, or sensitivity to touch on your right side below your ribs
- yellow skin or whites of your eyes

Nevirapine can cause serious skin rash. Skin rash is the most common side effect of nevirapine. Most rashes occur in the first 6 weeks of treatment. In a small number of patients rash can be serious and result in death. **Therefore, if you develop a rash with any of the following symptoms, you must stop taking the medicine and tell your doctor immediately.**

- general ill feeling or “flu-like” symptoms
- fever
- muscle or joint ache
- tiredness
- conjunctivitis (red or inflamed eyelids, like “pink-eye”)

- blisters
- mouth sores
- swelling of your face

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking Apo-TriAvir you must **stop** taking the medicine and tell your doctor **immediately**.

- sudden wheeziness and chest pain or tightening
- swelling of eyelids, face or lips
- skin rash or ‘hives’ anywhere on the body
- very severe stomach cramps

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Consult your doctor at your next visit if any of the following undesirable events occur:

Headaches, nausea, vomiting, diarrhea, fever, rash, fatigue, a general feeling of being unwell, or a numbness, tingling sensation or sensation of weakness in your limbs.

Apo-TriAvir may also cause a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and increase in certain liver tests.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Always tell your doctor or pharmacist about any undesirable effects, even those not mentioned on this leaflet.

If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

This is not a complete list of side effects. For any unexpected effects while taking ^{Pr}Apo-TriAvir, contact your doctor or pharmacist.

HOW TO STORE IT

Store Apo-TriAvir tablets between 15° and 30°C. Protect from light.

As with all medicines, keep Apo-TriAvir out of reach of children.

Do not take your medicine after the expiry date shown on the bottle and the carton.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadrmp@hc-sc.gc.ca

By regular mail:

Canadian Adverse Drug Reaction Monitoring Program

(CADRMP)

Health Canada

Address Locator: 0201C2

Ottawa, ON K1A 1B9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional. This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service, at 1-800-667-4708. This leaflet can also be found at <http://www.apotex.ca/products>.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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